ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

VOLUME 66, ART. 4 PAGES 841–1022

ANESTHESIOLOGY AND RELATED PROBLEMS

BY

C. R. STEPHEN and E. J. DE BEER (*Conference Co-Chairmen*), D. M. AVIADO, JR., C. M. BARBOUR, C. L. BURSTEIN, V. J. COLLINS, B. M. COOPER, R. FRAYSER, J. S. HARRIS, S. G. HERSHEY, J. B. HICKAM, D. M. LITTLE, JR., J. V. MALONEY, JR., E. V. NEWMAN, E. M. PAPPER, R. T. PATRICK, J. W. POPPELL, W. W. PRYOR, H. T. RANDALL, K. E. ROBERTS, H. O. SIEKER, W. A. SPENCER, P. VANAMEE, J. L. WHITTENBERGER, and B. W. ZWEIFACH

NEW YORK

PUBLISHED BY THE ACADEMY

April 2, 1957

THE NEW YORK ACADEMY OF SCIENCES

(Founded in 1817)

COUNCIL, 1957

President
ROSS F. NIGRELLI

President-Elect
BORIS PREGEL

Vice-Presidents
EDWARD J. KEMPF
HILARY KOPROWSKI

Recording Secretary
EMERSON DAY

Corresponding Secretary
FREDERICK C. NACHOD

Treasurer
ROBERT F. LIGHT

Elected Councilors

1955–1957
M. J. KOPAC
C. P. RHOADS
LLOYD C. MILLE
ELMER L. SEVERINGHAUS

1956–1958
DONALD B. KEYES
WARREN O. NELSON
CHARLES D. MARPL
FREDERICK Y. WISELOGLE

1957–1959
GEORGE H. MANGUN
MINA REES
HAYDEN C. NICHOLSO
WILLIAM W. WALCOTT

Finance Committee
HARDEN F. TAYLOR, *Chairman*
GORDON Y. BILLARD
JOHN TEE-VAN

Executive Director
EUNICE THOMAS MINER

SECTION OF GEOLOGY AND MINERALOGY
M. HALL TAYLOR, *Chairman*
ANASTASIA VAN BURKALOW, *Secretar*

SECTION OF BIOLOGY
ALBERT S. GORDON, *Chairman*
LOUIS G. NICKELL, *Secretar*

DIVISION OF MYCOLOGY
M. L. LITTMAN, *Chairman*
KARL MARAMOROSCH, *Secretar*

SECTION OF PSYCHOLOGY
RALPH F. HEFFERLINE, *Chairman*
ELAINE GRIMM, *Secretar*

SECTION OF ANTHROPOLOGY
MARGARET MEAD, *Chairman*
DOROTHY CROSS JENSEN, *Secretar*

SECTION OF PHYSICS AND CHEMISTRY
ROBERT NEILSON BOYD, *Chairman*
JOSEPH GREENSPAN, *Secretar*

SECTION OF OCEANOGRAPHY AND METEOROLOGY
JEROME SPAR, *Chairman*
EDWIN L. FISHER, *Secretar*

SECTION OF MATHEMATICS AND ENGINEERING
PAUL HARTMAN, *Chairman*
NICHOLAS V. FEODOROFF, *Secretar*

Past Presidents
WILLIAM K. GREGORY
VICTOR K. LAMER
HORACE W. STUNKARD
M. L. CROSSLE
HARDEN F. TAYLO
M. L. TAINTE
WALTER S. ROOT

The Sections and the Division hold meetings regularly, one evening each month, dur ing the academic year, October to May, inclusive. All meetings are held at the buildin of The New York Academy of Sciences, 2 East Sixty-third Street, New York 21, Ne York.

Conferences are also held at irregular intervals at times announced by specia programs.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

VOLUME 66, ART. 4 PAGES 841-1022

April 2, 1957

Editor in Chief
OTTO V. ST. WHITELOCK

Managing Editor
FRANKLIN N. FURNESS

ANESTHESIOLOGY AND RELATED PROBLEMS *

Conference Co-Chairmen: C. R. STEPHEN and E. J. DE BEER
Consulting Editor: C. R. STEPHEN
Associate Editor: MARGARET P. CAMERON

CONTENTS

* This series of papers is the result of a conference on *Anesthesiology and Related Problems* held by the Section of Biology of The New York Academy of Sciences, May 18 and 19, 1956.

Part I. Geriatric Anesthesia

INTRODUCTION

By Vincent J. Collins, *Chairman*
St. Vincent's Hospital, New York, N. Y.

Since birth we have all been subject to the mysterious process of aging, which is a universal phenomenon. It is certain that it is not simply a matter of "running downhill," because many functions are preserved at a normal basal level, for example, mechanisms for maintaining acid-base balance and carbohydrate homeostasis. We must also distinguish between senility *per se* and the condition of the older person who is afflicted only with the various disease processes customarily encountered. In reality, it is impossible completely to separate the disease processes from the changes that take place with the passage of time. Aging in the absence of disease is an abstraction. Therefore, a precise definition of aging encounters certain semantic difficulties. Arbitrarily, we can take the age of 60 years as the time at which the application of geriatric medicine is first required. We can, however, appreciate the concept of geriatrics without creating inflexible limits.

Aging may be considered both as a dynamic organic and as a dynamic functional process.

(1) Organically, aging involves those intrinsic changes that result in a lessened capacity of the tissue to multiply or in a decreased capacity for self-duplication or restoration of anatomical continuity.

(2) Functionally, aging reflects those intrinsic changes that result in a lessened capacity for adjustment to the environment and a decreased ability to compensate for stress.

The proportion of the aged in the population of the United States is rapidly growing, due to the gradual increase in life expectancy: in 1900 this was 48 years; in 1950 it had become 68 years. Of greater importance to anesthesiologists is the fact that the proportion of patients over 60 undergoing surgery has risen from 10 per cent in 1935 to 25 per cent in 1950.

Anesthesia for the aged patient is often an empirical modification of procedures accepted for the young patient. Proper evaluation of the present results is required to determine the correctness of this approach.

NUTRITIONAL AND HEMATOLOGICAL FACTORS IN GERIATRIC ANESTHESIA

By Charles M. Barbour

Department of Anesthesiology, Hartford Hospital, Hartford, Conn.

The purpose of this presentation is to emphasize the important role that anesthesiologists must assume in the evaluation, preparation, and management of geriatric patients. Recognition of all the factors that contribute to physiological imbalance is essential to the optimal preparation of elderly patients for anesthetic and operative procedures. All available means should be employed to assure detection and to promote correction of existing abnormalities before elective operations are performed.[1, 2] Even in emergencies, surgery should be deferred, whenever possible, to permit the administration of corrective or prophylactic therapy. Achievement of these objectives requires a replacement therapy to restore the body's total complement of circulating blood, electrolytes, minerals, and nutritional factors. Remarkable improvements in the rates of morbidity and mortality have been achieved as a result of the development of modern anesthesiology, the discovery of chemotherapeutic agents and antibiotics, and the availability of blood, blood fractions, and plasma substitutes. The resulting increased longevity provides us with the opportunity to bring about further reductions in morbidity and mortality rates by definitive therapy employed to correct specific deficits. This can be accomplished if reductions in the volume of blood and other fluids, and in protein, electrolytes, and minerals are replenished according to the total requirements of the body, as demonstrated by reliable laboratory procedures and considered in the light of the patient's clinical condition.

Deleterious effects caused by nutritional deficiencies and by abnormalities of blood volume constitute the commonest factors that jeopardize the ability of geriatric patients to tolerate performance of operative procedures.[2] Correction of minor as well as major deficits of blood volume, hypoproteinemia, fluid and electrolyte imbalance, and avitaminosis has a definite influence in reducing the incidence of operative and postoperative shock, infection, and faulty healing of wounds. If allowed to continue uncorrected, these conditions lead to the development of serious complications due to impaired function of the cardiovascular, respiratory, hepatic, renal, and central nervous systems. Although signs and symptoms of the presence of these deficiencies may not be evident, all geriatric patients must be approached with the attitude that one or more of these abnormalities may exist. The most treacherous patients to manage are those whose deficits are masked because of coexisting abnormalities.

Marked alterations of physiological function may develop during or following anesthesia and surgery if concealed deficits remain unrecognized and uncorrected. Potential deficiencies become real, and existing abnormalities are accentuated. Unless optimal physiological function is achieved

before geriatric patients are subjected to the hazards of anesthesia and operation, limitations of reserve function may make it impossible for them to cope with added stress. The time to correct abnormalities of blood volume and nutrition is prior to operation. We have achieved greater progress in eliminating the hazards of anemia than in correcting hypoproteinemia.

The necessity and value of replenishing deficits of blood volume and protein according to the quantitative and qualitative needs of surgical patients are especially applicable to those who are chronologically or physiologically aged.[3] Manifestations of pathological physiology among patients below the age of 65 years make it obvious that no clearly defined dividing line differentiates geriatric patients from those who are prematurely aged. Special consideration must be given to elderly patients whose existing abnormalities are further complicated by the presence of acute or persistent hemorrhage, chronic loss of blood, compensated anemia, or chronic uncompensated hypovolemia (Lyons' syndrome of chronic shock). Many of the pitfalls of geriatric care can be avoided if the replenishment of deficits in the volume of plasma, of red blood cells, or of whole blood is guided by studies of blood volume (FIGURE 1). Because the chronologically and physiologically aged patients are very likely to have multiple abnormalities, correction of all factors possible is essential.

Acute Hemorrhage

Major problems of the anesthetic management of geriatric patients are created by the presence of acute or persistent hemorrhage. The anesthesiologist must have a thorough knowledge of the physical status of geriatric patients in order that he may take a firm stand with regard to their ability or inability to tolerate surgery. Although impairment of reserve function reduces their capacity to respond to acute loss of blood, the prompt ad-

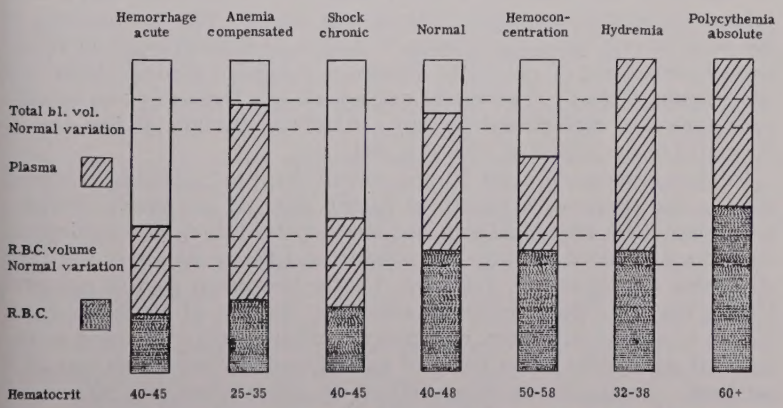

FIGURE 1. Schematic representation of common abnormalities of blood volume.

ministration of adequate amounts of whole blood usually produces favorable results. However, if hemorrhage remains untreated, if it is persistent, or if it occurs in the presence of pre-existing anemia, dehydration, or hypoproteinemia, the defense mechanisms of vasoconstriction or hemodilution may not be able to compensate for the deficits. In these situations, the absence of reliable guides to quantitative replacement therapy can cause tragic errors. The conservative practitioner may administer too little whole blood, while the enthusiast may overload the patient. Studies of blood volume will not only facilitate intelligent replacement therapy following acute or persistent hemorrhage, but will provide clues to the possible presence of pre-existing anemia, dehydration, or hypoproteinemia.

These considerations must be borne in mind during the management of replacement therapy in states of emergency. This is especially true when studies of blood volume are not available. Pre-existing abnormalities contribute to the inability of patients to respond to therapy and, not infrequently, they cause accentuation of the severity of circulatory collapse.[4] Onset of congestive failure may result if replacement therapy is too vigorous for patients with potential or existing myocardial insufficiency. Faulty blood-clotting mechanism contributes to the continuation of hemorrhage in the presence of disease of the liver. In the absence of specific therapy, adrenal insufficiency causes continued hypotension, irrespective of the administration of supportive therapy other than cortisone.

Compensated Anemia

Compensated anemia is probably the most common abnormality of blood volume encountered among geriatric patients (FIGURE 2).

Provided that fluid and electrolyte balance are within normal limits, the presence of hemorrhage will initiate the process of hemodilution. Passage of interstitial fluid into the vascular bed soon restores the body's total volume of circulating blood.[5] This is true whether the loss of blood is due to acute or chronic hemorrhage, to failure of hematopoiesis, or to abnormal destruction of red cells. Failure to recognize the importance and effectiveness of this compensatory mechanism is a frequent cause of mismanagement of replacement therapy. A typical example of this fact is illustrated in the following clinical report.

R. H., a 69-year-old obese female, was admitted to hospital in profound shock. She presented a history of gastric ulcer of one year's duration, with intermittent abdominal pain, and tarry stools of three weeks' duration. Recordings of blood pressure and pulsations of the radial artery were not obtainable on admission. The value for the hematocrit was 16 per cent. During the first 5 hours following admission, 2000 cc. of whole blood and 250 cc. of normal saline were administered intravenously. The next morning vital signs were within limits of normal, and the hematocrit was 31.5 per cent. During the morning 500 cc. of whole blood and 500 cc. of normal saline were administered. That evening one unit of packed red

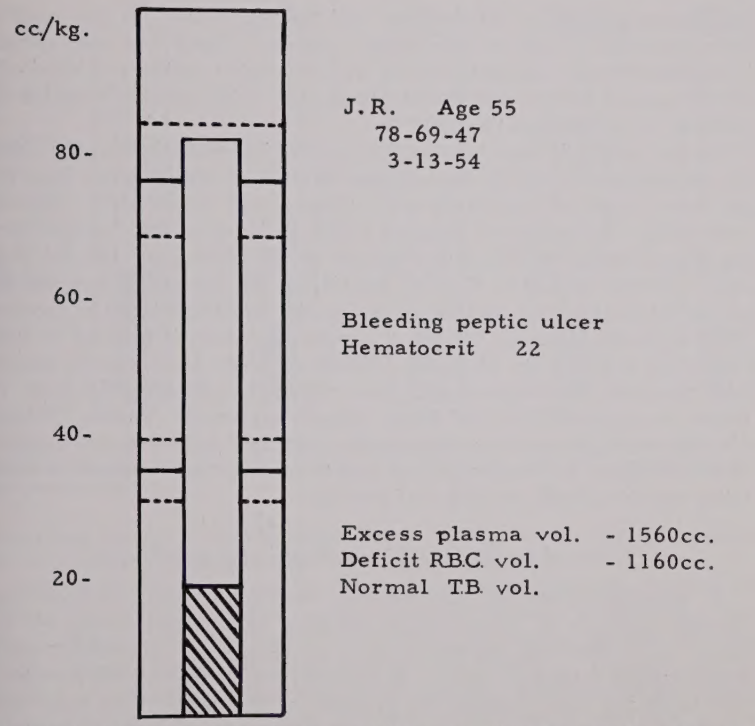

FIGURE 2. Typical example of compensated anemia. Note the excessive volume of plasma necessary to restore total blood volume to normal.

blood cells was given. At 8:30 P.M. of this second hospital day the patient was again in profound shock. Administration of 1000 cc. of whole blood failed to correct the severe degree of circulatory collapse. After an additional 500 cc. of whole blood were given, the patient's condition improved somewhat. As the fifth transfusion of the day was begun, the patient was taken to the operating room for performance of emergency subtotal gastrectomy. During the operation 1000 cc. of whole blood and 1000 cc. of other fluids were given. Recordings of blood pressure rose from shock levels, during the early part of the operation, to low levels of normal toward the conclusion of the emergency procedure. (TABLE 1.)

When the patient was in the recovery room she received 500 cc. of 5 per cent dextrose in distilled water. Soon after an infusion was initiated the following morning, the patient developed severe pulmonary edema. Administration of morphine, digitalis, and oxygen under intermittent positive pressure, and performance of phlebotomy were required. Response to the therapy was slow, but the patient recovered. Administration of

injudicious amounts of whole blood and fluid accounted for the onset of left ventricular failure in this elderly patient. There had been definite indications for the administration of transfusions of packed red blood cells to this patient because her initial hematocrit of 16 per cent revealed the presence of compensated anemia.

Greater emphasis must be placed on correct interpretations of the values for the hematocrit and on the influence exerted by hemodilution upon this and other tests of concentration.[5] During and immediately following hemorrhage the hematocrit remains within limits of normal because there are proportionate deficits in the volumes of the plasma and the red blood cells. Within from 4 to 8 hours, fluid from the interstitial compartment enters the vascular tree, and the values for the hematocrit begin to decrease. By this process alone the volume of circulating plasma is restored to limits of normal within 12 to 24 hours. Before 48 hours have elapsed, patients with adequate fluid balance will have obtained sufficient fluid from the tissues to replenish the total blood volume to normal. Within 72 hours after hemorrhage, patients who remain untreated following acute loss of blood are likely to overcompensate and to possess total volumes of circulating blood markedly in excess of normal.

Hemorrhage and the Three Phases of Hemodilution

If no transfusions are administered, the healthy individual will pass through 3 phases of hemodilution following hemorrhage (FIGURE 3 and TABLE 2). When the normal volume of plasma is replenished, partial compensation (phase I) exists. Moderately low values for the hematocrit (30 to 34 per cent) indicate the presence of this phase. The total blood volume remains deficient. Phase II, or compensated anemia, is characterized by the presence of excessive volumes of circulating plasma and the restoration of the total blood volume to normal. Values for the hematocrit range from 20 to 30 per cent. Phase III, or overcompensation, exists when very low values for the hematocrit (10 to 20 per cent) indicate the presence of excessive total blood volume, with a marked excess of plasma volume, and a deficit in the volume of the red cells. As is true of values for the hematocrit after hemorrhage, reductions in the concentration of

TABLE 1

Date	Whole blood	Packed red blood cells	Other fluids
5/ 8/56	2000 cc.	0	250 cc. normal saline
5/ 9/56	2000 cc.	250 cc.	500 cc. normal saline
5/10/56*	1000 cc.	0	1500 cc.
5/11/56†	0	0	500 cc.
5/14/56	Hct. 52	Protein 5.4	
5/16/56	Hct. 50.5		

Results of blood volume studies: 61-gm. deficit of protein; 500-cc. deficit of plasma; 300-cc. excess of red blood cells; total volume of blood—normal.

* Subtotal gastrectomy.
† Left ventricular failure; pulmonary edema; phlebotomy.

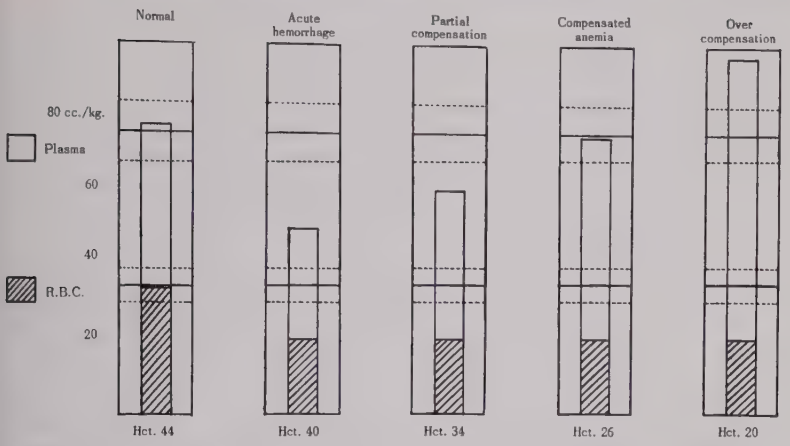

FIGURE 3. Hemorrhage with phases of hemodilution. Schematic representation to illustrate the sequence of events following loss of blood for which no transfusions have been administered.

circulating protein following acute loss of blood are not reflected by tests of concentration until hemodilution has taken place.

Although the body's protective mechanisms will restore the volumes of plasma and of total blood to normal, considerable time is required to replenish deficits in the volume of the red blood cells and in protein. Balance can be restored by the administration of transfusions of red cells and by the oral or intravenous administration of protein. Erythrocytes are not an immediate source of protein because this component of the cells is not available until the expiration of their 120-day life cycle.[16] For patients who are unable to ingest food, the intravenous administration of protein hydrolysates provides the body with the essential building blocks[16] to reestablish nitrogen balance. It has been estimated that a reduction of tissue protein amounting to 30 gm. takes place before there is a deficit of 1 gm. of total circulating protein in the plasma.[17, 18] Conversely, 30 gm. of protein must be deposited in the tissues before 1 gm. is retained in the plasma. These facts warrant greater emphasis.

Administration of packed red blood cells is indicated in all the phases of compensation described in which the volumes of plasma and of total blood are restored while the deficit of red blood cells persists. In the

TABLE 2

PHASES OF HEMODILUTION TO COMPENSATE FOR LOSS OF BLOOD

	Classification	Plasma vol.	RBC vol.	Total blood vol.
Phase I	Partial compensation	Normal	Reduced	Reduced
Phase II	Compensated anemia	Excess	Reduced	Normal
Phase III	Overcompensation	Marked excess	Reduced	Excess

absence of hydremia (found in cirrhosis of the liver, in renal insufficiency, and in cardiac failure) values for the hematocrit below 30 per cent are definite indications of the presence of compensated anemia, and the use of specific replacement therapy should be guided by studies of blood volume. The treatment of compensated anemia must be qualitative as well as quantitative. Younger patients may be able to withstand the untoward effects of circulatory overload caused by injudicious replacement therapy; the geriatric patient, however, is prone to develop serious complications. Administration of definitive therapy eliminates the potential complications of pulmonary edema, congestive failure, and the hazard of localized edema, which may lead to the disruption of suture lines at the site of intestinal anastomoses and to the faulty healing of other wounds. In the presence of compensated anemia, hemodilution exaggerates the magnitude of existing anemia,[2, 3] but facilitates the maintenance of circulatory function during anesthesia and surgery. Onset of shock is therefore not as probable as it is in the presence of chronic hypovolemia. The real hazard is the production of circulatory overload.

Chronic Uncompensated Hypovolemia

Patients with chronic uncompensated hypovolemia (FIGURE 4) are notoriously susceptible to circulatory collapse when they are subjected to the added stress of anesthesia and operation.[1, 3, 6] In the presence of peripheral vasodilatation or hemorrhage the existence of proportionate reductions in the volumes of plasma and of red blood cells favors the onset of hypotension. Additional loss of minimal amounts of blood precipitates the onset of shock—a characteristic finding during surgery for patients with this syndrome. In addition to reductions in the volume of plasma and red cells there are deficits of tissue and plasma protein and an increased volume of fluid within the interstitial compartment. These factors make it impossible for normal defense mechanisms of the body to compensate for reduced volumes of blood (for this reason the author favors the more descriptive term "chronic uncompensated hypovolemia," rather than "chronic shock"). The ability to respond to further stress, for example, to combat infection, is impaired, as is the capacity to repair wounds. Among these patients, values for the hematocrit, concentration of serum protein, and other tests of concentration are normal despite the presence of significant deficits of blood volume. It is therefore essential that one maintain a high degree of clinical suspicion with regard to the possible presence of this syndrome among geriatric patients. Chronic hypovolemia is frequently found among patients with malnutrition, chronic infection, malignancies of the gastrointestinal tract (especially the stomach and colon), and metastatic disease (TABLE 3). Studies of blood volume and determination of the total amount of circulating protein facilitate quantitative replenishment of deficits of whole blood and the administration of protein hydrolysates prior to operation. Our experience has been in keeping with the contention expressed

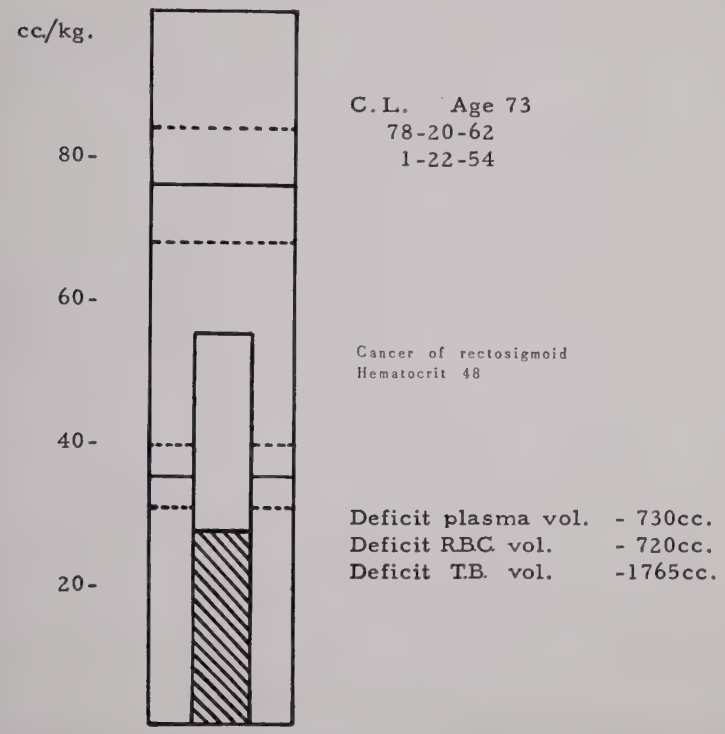

FIGURE 4. Typical illustration of chronic shock or chronic uncompensated hypovolemia. Note the proportionate reductions in the volumes of plasma and of red blood cells.

TABLE 3

PREOPERATIVE BLOOD VOLUMES IN 200 PATIENTS WITH PROVED CARCINOMA

Site	Normal	Chronic shock	Compensated anemia
Colon	19	33	33
Stomach	12	20	15
Lung	10	3	7
Esophagus	6	4	1
Genitourinary	4	6	3
Gynecological	4	1	7
Miscellaneous	3	6	3
Total	58	73	69
Percentage	29%	36.5%	34.5%
		71%	

by Whipple that, in the presence of deficits of hemoglobin and tissue protein, synthesis of hemoglobin receives priority over the manufacture of tissue proteins.[7, 8] Replenishment of deficits of whole blood for patients with chronic hypovolemia promotes the restoration of deficiencies of protein by permitting deflection of the available amino acids to the synthesis of tissue and plasma protein.

Hemoconcentration and Shifts of Electrolytes

Values for the hematocrit vary with the pre-existing clinical status of each patient with regard to fluid balance, the volume of various components of circulating blood, and the presence of acute or chronic disease. Because of the high incidence of factors that lead to hemoconcentration and hypervolemia among elderly patients, the presence of these conditions must receive serious consideration and attention.[9, 10] Inadequate intake or utilization of food and fluids is a common finding among elderly patients. Inadequate nutrition not only contributes to the development of deficiencies of metabolism and electrolyte imbalance, but subjects these individuals to the hazards of circulatory insufficiency and thrombosis due to increased viscosity of the circulating blood. Hemoconcentration accompanies many disease processes. As with anemia or hypoproteinemia, its presence may precipitate the appearance of severe complications. When the loss of fluid due to perspiration is excessive, latent disease processes may become real, and existing pathology may be aggravated. When hemoconcentration is superimposed upon arteriosclerosis or heart disease, thrombosis of cerebral, myocardial, or other vital vascular channels may result.

In the presence of peritonitis and dehydration due to perforated peptic ulcer, Cope *et al.* emphasize the importance of immediate restoration of the circulating volume of plasma before the performance of surgical closure in an emergency.[11] Among these patients, the onset of dehydration is rapid and severe. The characteristic pattern of electrolyte imbalance developed during the immediate postoperative period contraindicates the administration of saline except in restricted amounts. A shift of sodium and chloride from the circulation to the peritoneum is associated with the onset of edema that persists for approximately 3 days. Contrary to former beliefs, the administration of sodium and chloride in amounts that exceed external losses only aggravates the edema of the peritoneal surfaces and prolongs the period of salt retention. Within 3 to 6 days the edema subsides without treatment, and the retained sodium, chloride, and water are reabsorbed. During the first 3 days the total amount of these ions in the circulating blood is reduced because of dehydration. Reabsorption of the salt-containing edema fluid after the second postoperative day accounts for the presence of increased amounts of sodium and chloride in the blood during the period of salt elimination. With the onset of edema a greater proportion of water than salt is retained in the tissues. When edema subsides, the kidneys excrete larger amounts of water than of salt, thereby

conserving the body's supply of electrolytes. Replenishment of existing deficits of plasma bolsters the ability of these dehydrated patients to tolerate anesthesia and operation, anticipates losses due to peritonitis, and satisfies some of the nutritional needs during convalescence.

Whereas no attempt should be made to maintain the concentration of serum sodium immediately following the closure of a perforated ulcer, the replacement of potassium should be vigorous. Daily administration of approximately 75 mEq. of potassium is required to replace external losses of this essential intracellular ion. Correction of existing deficits of potassium eliminates one of the major factors that contribute to a high mortality among patients with perforated ulcers and peritonitis.

The concept of specific replacement of all the components of the circulating blood is equally valuable when applied to electrolyte therapy. Knowledge of the total amount of circulating sodium or potassium is most helpful in the management of patients with fluid and electrolyte imbalance, especially in cases of intestinal obstruction, peritonitis, cirrhosis of the liver, cardiac failure, dehydration, renal insufficiency, and disorders of endocrine function. Quantitative studies of the distribution of electrolytes are valuable in determining whether decreased concentration of sodium, for example, is the result of depletion of salt, of retention of water, or of a shift of the ion into the cells as a consequence of depletion of potassium.[12]

Application of this concept will provide great assistance in the management of replacement therapy for patients receiving prolonged administration of cortisone, especially those who develop intestinal obstruction, peritonitis, or congestive failure.[13] Retention of sodium and increased excretion of potassium and nitrogen are characteristic pharmacological actions of cortisone[14] and administration of this substance may accentuate any abnormal distribution or elimination of these elements. These properties of cortisone, together with its capacity to mask the subjective and objective responses of the body to the presence of infection, sometimes lead to preventable fatalities among surgical patients.

Hypervolemia

Patients with a long history of hypoxia due to asthma, chronic bronchitis, emphysema, pulmonary fibrosis, or chronic heart disease should be suspected of having secondary polycythemia (FIGURE 5). In the presence of signs and symptoms of hypervolemia and/or hemoconcentration, studies of blood volume should be made to differentiate between dehydration and polycythemia.[9, 10] If necessary, elective procedures should be postponed in order to carry out such studies and to permit the institution of corrective measures. These precautions will avoid placing an added burden upon the patient's already overtaxed cardiovascular and respiratory systems. The presence of hypervolemia and hemoconcentration increases the hazards of general anesthesia, causes excessive bleeding from incised or traumatized areas, and favors the development of thrombotic and embolic complications.

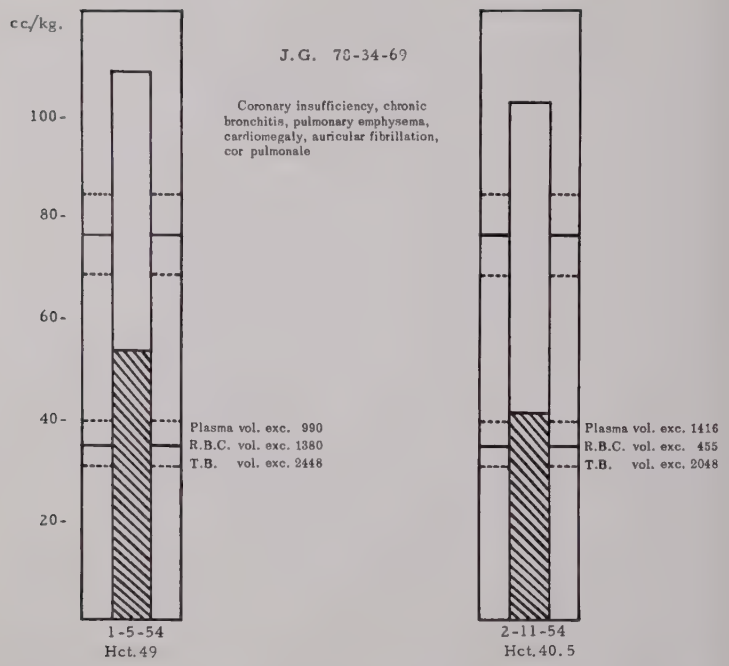

FIGURE 5. Secondary polycythemia in the presence of normal values for the hematocrit among patients with chronic pulmonary or chronic heart disease.

The function of vital structures is further impaired. The slowing of the circulation may precipitate the onset of thrombosis of the coronary or cerebral vessels. (The lowest values recorded for the cerebral blood flow, 22 ml./100 gm. brain/min., were due to the increase in cerebrovascular resistance caused by increased viscosity in the presence of polycythemia).[15] The performance of phlebotomies under controlled conditions prior to operation will avoid the complications due to hypervolemia and increased viscosity. The induction and maintenance of optimal planes of general anesthesia are facilitated; increased bleeding into the wound during and following operation is prevented; the incidence of thrombophlebitis and other thrombotic phenomena is reduced; and the hazards of circulatory overload, congestive failure, pulmonary edema, and cerebral edema are eliminated.

In the presence of marked malnutrition, anesthesiologists and surgeons are likely to be aware of the possible existence of anemia, acute or chronic infection, and malignant disease. However, the presence of disease of the liver may be overlooked.[20] Enumeration of the multiple functions of the liver emphasizes the importance of considering the urgency of a contem-

plated operation, the magnitude of the procedure to be performed, and the degree of nutritional deficiency that may exist among patients having hepatic dysfunction.[21] The liver is the pre-eminent organ of metabolism. Glycogen, proteins, vitamins, and antipernicious anemia factors are stored in the liver. Plasma, fibrinogen, prothrombin, and heparin are synthesized by it, and it is here that bile is secreted. Other important functions include the formation and destruction of erythrocytes, the production of antibodies, and the detoxification of noxious agents. When its stores of carbohydrate and protein are ample, the function of the liver enables the body to resist many forms of stress. When loaded with fat its efficiency is impaired.[22] Depression of the functional activity of the liver renders the body more susceptible to nutritional disturbances by reducing its capacity to store, to synthesize, to secrete, and to detoxify. Conversely, disturbances of nutrition make the liver more vulnerable to the untoward effects of noxious agents. Multiple factors contribute to the decreased ability of patients with hepatic dysfunction to tolerate anesthesia and operation. These patients are not only likely to be anemic, but may bleed profusely due to the presence of a faulty mechanism of coagulation. Intestinal motility is disturbed, and these patients are prone to develop ileus. These factors, together with the increased susceptibility of the patients to infection, edema, and shock, make such cases poor risks.

Prior to the performance of elective or emergency procedures one should evaluate the geriatric patient with respect to degree of nutritional deficiencies and the possible presence of impaired function of the liver. Clinical or subclinical nutritional deficiencies produce physiological changes that become manifest, or are accentuated, by the administration of anesthetic agents and the performance of operative procedures. Correction of every known abnormality prior to operation is the major factor in minimizing morbidity and mortality. Diets high in protein and caloric content constitute an important part of the preoperative preparation of patients with malnutrition. The most effective method of replenishing deficits of protein is administration by the oral route.

Fracture of the Hip

Fracture of the hip is a typical major accident of the aged. Patients suffering from such fractures have been selected for discussion because many of them possess one or more of the complicating factors I have mentioned. Most of these patients are in the geriatric group. Not infrequently their fractures are the result of injuries caused by pre-existing infirmities (such as malnutrition, anemia, or disease of the cardiovascular or central nervous systems) that produce dizziness, faintness, and collapse. These facts must be considered in the clinical evaluation of the patient and in the selection of the agents and techniques to be employed for anesthesia. The amount of concealed hemorrhage that may follow fractures of the femur should be emphasized. As much as 1500 cc. of blood may be present in

Table 4

Failure of Hematocrit Values to Indicate Deficits in Volumes of Plasma, of Red Blood Cells, or of Total Blood Among 111 Geriatric Patients with Fracture of the Hip

Deficits in cc.	Hct. 40+	Hct. 39 to 30	Hct. 29—
Plasma vol.			
300–1000	21	18	8
1000–1500	4	0	0
1500–2000	—	—	—
R.B.C. vol.			
300–1000	17	44	2
1000–1500	0	9	8
1500–2000	0	0	0
Total blood vol.			
300–1000	16	27	1
1000–1500	6	17	5
1500–2000	0	1	1

the tissues of the hip and thigh without outward evidence of its presence. Losses of blood of this magnitude occurring in the presence of pre-existing anemia or other abnormalities seriously jeopardize the ability of these patients to tolerate anesthesia and operation. Deficits of blood volume are partially responsible for the incidence of major degrees of hypotension that may be precipitated by the administration of spinal anesthesia to these patients. When there are no studies of blood volume, the magnitude of existing anemia among patients with fractures of the femur is frequently unrecognized.

Transient deficits of nitrogen among normal patients are of little consequence, but the increased excretion of nitrogen following traumatic injury to debilitated patients frequently results in severe depletion. Patients with fracture of the hip provide excellent examples of this fact. Markedly increased excretion of nitrogen may persist for as long as 4 to 6 weeks following such severe trauma.[17] A preliminary report of determinations of blood volume for 111 patients with fracture of the femur is presented to emphasize the high incidence of anemia and hypoproteinemia (table 4). A report of determinations of blood volume for 317 patients over 70 years of age provides comparable information (tables 5 and 6).

Table 5

Failure of Hematocrit Values to Indicate Deficits in the Volumes of Plasma, of Red Blood Cells, or of Total Blood Among 317 Patients Aged 70 or Over

Deficits in cc.	Hct. 40+	Hct. 39 to 30	Hct. 29—
Plasma vol.			
300–1000	33	24	7
1000–1500	9	2	0
1500–2000	0	1	0
R.B.C. vol.			
300–1000	33	79	16
1000–1500	2	18	23
1500–2000	0	0	6
Total blood vol.			
300–1000	27	38	14
1000–1500	13	25	5
1500–2000	6	4	4

Table 6

Statistics Emphasizing the High Incidence of Significant Deficits of the Various Components of Circulating Blood Among Geriatric Patients

Deficits	317 Patients (all types)	111 Patients (fractures of hip)
Plasma volume, 300–2000 cc.	24%	46%
R.B.C. volume, 300–2000 cc.	56%	72%
Total blood vol., 300–2000 cc.	40%	66%
Plasma protein	30%	45%

Analysis of the results of these two series emphasizes the following facts: (1) values for the hematocrit and other tests of concentration are not indicative of existing deficits or excesses of blood volume; (2) significant reductions or excesses of plasma and red-cell volume may coexist in the presence of normal values for the hematocrit; (3) low values for the hematocrit give an exaggerated picture of the degree of existing anemia, but may indicate the possible presence of hydremia; (4) pathological hydremia (in cirrhosis of the liver, renal insufficiency, circulatory overload, and blood dyscrasias), hemoconcentration, and polycythemia are detected by studies of blood volume; (5) studies of blood volume alone can provide information about the specific needs of patients with regard to amounts and types of blood and blood substitutes, and can indicate the amount of circulating protein required to replenish deficits; (6) among normal patients, reduction of total blood volume by 30 per cent is accompanied by the onset of shock; (7) loss of smaller amounts of blood produces collapse of circulatory function in patients with existing deficits of blood volume; (8) studies of blood volume are of great value in the differential diagnosis of circulatory insufficiency produced by causes other than loss of blood (adrenal insufficiency, dehydration, overwhelming infection, and the like); (9) the administration of packed red cells, or of red cells suspended in saline or glucose, prevents the appearance of hypervolemia among patients with compensated anemia; and (10) the healthy young patient may tolerate the hypervolemia caused by the administration of transfusions of whole blood in the presence of compensated anemia: such injudicious therapy in geriatric patients, however, is likely to produce pulmonary edema, cerebral edema, and cardiac failure.

Conclusions

A definite parallelism exists between the untoward effects caused by anemia and hypoproteinemia. The presence of either condition may be concealed by the absence of obvious clinical manifestations. The existence of one deficiency leads to development of the other. Unless specific laboratory procedures are performed, the presence of these deficiencies may remain unrecognized. In operative and postoperative management the existence or coexistence of hypovolemia and hypoproteinemia may seriously impair physiological function and may account for continued preventable morbidity and mortality. Apart or together, these deficiencies and the

presence of electrolyte imbalance can lead to the development of vicious cycles that cause progressive decline of vital function and even demise.

Hematopoiesis and normal synthesis of protein cannot be restored when the activities of the tissues are impaired by inadequate oxygenation and lack of essential nutrients. When tissue cells are surrounded by an abnormal environment, cellular function is reduced or absent. Excesses or deficits of blood, minerals, electrolytes, colloids, and proteins account for irreparable damage by breakdown of the vital exchange between the vascular, interstitial, and intracellular compartments. Administration of anesthesia to patients who fall into these categories must be postponed until remedial measures are instituted. Greater emphasis must be placed on avoidance of too hasty performance of surgical procedures for patients with potential or actual deficiencies of nutrition.

References

1. Tennant, R., L. Adelson, G. McAdams & R. Davie. 1950. The use of blood volume studies as a clinical aid in intravenous therapy. Yale J. Biol. Med. **22**(6): 735–745.
2. Barbour, C. M., Jr. 1953. Blood volume: An important factor in anesthetic management. Proc. Canadian Anaesthetists' Soc.: 18–23.
3. Barbour, C. M., Jr. & R. Tennant. 1954. Clinical application of blood volume studies in major surgery. J. Urol. **71**(4): 497–501.
4. Barbour, C. M., Jr. 1954. Circulatory failure: Some factors in its early recognition. Meeting Soc. Anesthesiologists. Cincinnati, Ohio.
5. Barbour, C. M. Jr. 1955. Value of blood volume determinations. Meeting Natl. Research Council. Subcommittee, Anesthesia Committee Med. & Surg. Washington, D. C.
6. Clark, J. H., W. Nelson, C. Lyons, H. S. Mayerson & P. DeCamp. 1947. Chronic shock: The problem of reduced blood volume in the chronically ill patient. Ann. Surg. **125**: 618.
7. Whipple, G. H. & S. C. Madden. 1944. Hemoglobin plasma protein and cell protein: Their interchange and construction in emergencies. Medicine. **23**: 215–224.
8. Madden, S. C., A. A. Kattus, J. R. Carter, L. L. Miller & G. H. Whipple. 1954. Plasma protein production as influenced by parenteral protein digests: Very high protein feeding and red blood cell catabolism. J. Exptl. Med. **82**: 181–191.
9. Barbour, C. M., Jr. 1950. Polycythemia in relation to anesthesia and surgery. Anesthesiology. **2**(2): 155–163.
10. Barbour, C. M., Jr. 1953. Blood volume: An important factor in preoperative evaluation. Conn. State Med. J. **17**(9): 747–750.
11. Cope, O. & A. Wight. 1956. Metabolic derangements imperiling the perforated ulcer patient. Arch. Surg. **72**(4): 571–582.
12. Leevy, C. M. & F. J. Donovan. 1955. Estimation of total circulating sodium. J. Am. Med. Assoc. **159**(8): 771–773.
13. Barbour, C. M., Jr. 1956. Hazards of deficiencies in endocrine function. Meeting New Engl. Soc. Anesthesiologists. Hartford, Conn.
14. Drill, V. A. 1954. Pharmacology in Medicine, A Collaborative Textbook. McGraw-Hill. New York, N. Y.; Toronto, Canada; London, England.
15. Elliott, K. A. C., I. H. Page & J. H. Quastel. 1955. Neurochemistry. Charles C. Thomas. Springfield, Ill.
16. Moore, F. W. & M. R. Ball. 1955. The Metabolic Response to Surgery. Charles C. Thomas. Springfield, Ill.
17. Zintel, H. S. 1955. Nutritional rehabilitation of the elderly patient undergoing surgery. Am. J. Clin. Nutrition. **3**(6): 501–510.

18. Sachar, L. A., A. Horowitz & R. Elman. 1942. Studies on hypoalbuminemia produced by protein deficiency diets. I. Hypoalbuminemia as a quantitative measure of tissue protein depletion. J. Exptl. Med. **75**: 453.
19. Wight, A., J. F. Hopkirk & O. Cope. 1956. Metabolic derangements imperiling the perforated ulcer patient. Arch. Surg. **72**(2): 336–345.
20. Williams, R. D. & R. M. Zollinger. 1955. Principles of surgical nutrition. Am. J. Clin. Nutrition. **3**(6): 449–455.
21. Barker, H. G. 1955. Supplementation of protein and caloric needs in the surgical patient. Am. J. Clin. Nutrition. **3**(6): 466–471.
22. Wright, S. 1953. Applied Physiology: 822–828. 9th ed. Oxford Univ. Press. London, England; New York, N. Y.; Toronto, Canada.

EVALUATION OF CARDIOVASCULAR COMPLICATIONS

By Elliot V. Newman

School of Medicine, Vanderbilt University, Nashville, Tenn.

In introducing my topic, I should like to point out that I am an internist and that, although the internist is interested in the results and complications of anesthesia, he can assume no real continuous responsibility for it.

The older patient has a narrower range of possible adjustments to stress. Change in blood volume is always a complication of surgery, and the evaluation of such change is of vital importance in the aged patient.

The methods in common use for determining blood loss during an operation are subject to error. Certainly the surgeon's usual estimate of blood loss is not to be trusted completely. Weighing the sponges may be more accurate. However, there is no better method of determining blood loss than the direct measurement of the quantity of blood remaining in the patient. It is particularly difficult to know if the blood volume is adequate in the early postoperative period when the wound is closed and there may be internal oozing.

While I do not recommend using chemical determinations to the exclusion of other clinical signs or of good clinical judgment, I believe it is indispensable in many cases to have an accurate measure of blood volume.

Blood-volume determinations can now be carried out, without an unreasonable expenditure of time and energy, by any physician familiar with standard laboratory procedures. It is possible to make accurate determinations of blood volume within 10 minutes and to repeat the determination several times without harm to the patient. The necessary equipment for the method that I shall describe can be set up on a tray beside the anesthesiologist. The total initial cost of the equipment and of the materials is similar to the cost of the apparatus used for blood chemical determinations in hospital laboratories.

The equipment consists of a well-type scintillation counter for radioactive iodine and a counting rate meter. The meter and the cuvette can be kept in the operating room and the electronic amplifier outside. A calibrated syringe is used to inject quantitatively a small amount of radioactive iodinated serum albumin into the patient's circulation. In 5 to 10 minutes a blood sample is withdrawn from the patient and placed in the counter. The amount of blood necessary is 2 to 5 cc., although the determination can be done on less if necessary. In 2 minutes the answer (the patient's blood volume) is read from a standard calibrated chart.

The determination of blood volume can be repeated easily at least 5 times without harmful radiation effects on the patient's thyroid. The amount of radioactive material employed would have less effect than the usual dose of radioiodine used for a routine tracer study in the diagnosis of thyroid dysfunction.

The radioactive iodinated serum albumin can be obtained in lots of

1000 mc. Because the half life of the preparation is 8.5 days, many determinations can be made with one lot, and it retains its usefulness over a period of a month.

Armed with this technique, one need never guess about the adequacy of a patient's blood volume. Often it is anticipated that an operation will entail considerable loss of blood. If this is expected, and if the patient is old and has a vulnerable cardiovascular system, a base-line control determination of blood volume can be made before operation to serve as a guide to replacement later. The diagnosis of too low or too high a blood volume may then be made with accuracy. Moreover, if repeated determinations are carried out after replacement therapy, the presence of internal hemorrhage may be more quickly and accurately ascertained if the blood volume continues to fall.

In the differential diagnosis of low blood volume, other causes of the signs and symptoms of shock must be considered. The primary signs are a change in pulse rate or rhythm, a fall in blood pressure, and a failure of peripheral circulation, revealed particularly by coldness, circulatory stasis, and cyanosis of the peripheral parts and skin.

I shall comment briefly on the following possible causes of signs other than blood loss: (1) paroxysmal cardiac arrhythmias; (2) reflex depression of cardiac activity; (3) chemical or metabolic depression of cardiac function; (4) reflex, chemical, or mechanical release or increase in peripheral resistance; (5) interference with venous return to the heart; (6) acute dilatation and failure of either or both chambers of the heart; (7) coronary insufficiency or myocardial infarction; and (8) abnormalities of adrenal function and of water, sodium, potassium, and protein metabolism.

Paroxysmal Cardiac Arrhythmias

The evaluation of cardiac arrhythmias by ordinary clinical signs may be quite difficult. One cannot distinguish between a paroxysmal rhythm of auricular origin and one of ventricular origin. Multifocal ventricular ectopic beats may give the same signs as auricular fibrillation, with its irregular ventricular response.

The internist properly feels that the evaluation of the heart in a patient beyond the age of 40 is not complete without an electrocardiogram. This would seem to be even more true of an older person laboring under the stress of anesthesia and surgery. There seems to be general agreement that cardiac complications are characteristic of the aged. Such statistics as those recently reported by Briggs, Sheldon, and Beecher[1] show that cardiac arrest is 20 to 30 times as frequent in aged people and should stimulate an alertness to these complications. It is too late to call for an electrocardiograph machine after cardiac arrest has occurred; indeed, if the patient is to be saved, such drastic measures as mechanical manual resuscitation of the heart, employment of electrical pacemakers, and the use of the defibrillator while maintaining respiratory exchange will be required. In this

paper I emphasize evaluation rather than therapy but, in the operating room, the procedures for evaluation are frequently modified under stress and by practical limitations.

To prevent such complications in aged patients, particularly those in poor condition, it would seem logical to have the electrocardiographic leads in place and the electrocardiograph monitoring machine in use before the initiation of anesthesia. There is no more accurate or rapid way to evaluate the origin and mechanism of an abnormality of cardiac rhythm.

From the standpoint of the internist, there are few things more frustrating than to be called suddenly to the operating room to help with a cardiovascular complication in a patient whom one has not seen previously. When the patient is aged, discussion of the problem and close co-operation among the anesthesiologist, the internist, and the surgeon are necessary; if the patient is a poor risk, it becomes the duty of the internist to attend the operation. The task of the anesthesiologist is already sufficiently heavy, and he cannot efficiently assume added burdens even in an emergency. I make these suggestions particularly for the benefit of the internist because, to fulfill his preoperative and postoperative advisory role, he should frequently have firsthand knowledge of events in the operating room.

Reflex Depression of Cardiac Function

Under this heading, I should mention the disorders of rhythm and rate of reflex origin. Traction and pressure by the surgeon in and around the abdominal viscera may cause temporary disturbances. Of more serious import are the reflex-initiated heart blocks and standstills that may be caused by stimulation of the carotid sinus and other depressor centers. Perhaps in aged people we should ascertain before operation and by a careful history and direct test the sensitivity of the carotid sinus mechanism.

Chemical or Metabolic Depression of Cardiac Function

The anesthesiologist is the person most capable of evaluating the depressing effect of anesthetic agents on cardiac function. Chemical or metabolic depression of myocardial function is the direct result of toxic effects of the anesthetic agent, of anoxia, and perhaps also of accumulation of carbon dioxide. The real proof of the presence of anesthetic depression, hypoxia, or CO_2 excess is the relief obtained by lightening the anesthesia and by increasing the respiratory exchange.

Decrease or Increase in Peripheral Vascular Resistance

A sudden decrease in peripheral resistance may occur when the surgeon opens the circulation to a previously occluded area. This is most strikingly illustrated during surgery of the aorta when reanastomosis is accomplished after excision of an obstruction or of an aneurysm. During surgery of the chest, changes in resistance in the pulmonary circulation may occur due to

collapse of the lung. In cardiac surgery, the closure of shunts may cause acute strain on segments of the circulation.

Interference with Venous Return to the Heart

Alterations of venous return may be effected by direct compression of the major venous channels; there may also be embarrassment to the circulation due to the position of the patient. The positional factors are the same as those that produce in the unanesthetized patient the symptoms and signs of orthopnea, paroxysmal dyspnea, and pulmonary edema. Shifts of blood volume and fluid into the central circulation may occur. The older patient with edema is particularly susceptible to such shifts. Postoperatively, the tilt of the bed frame may be a critical factor in maintaining circulatory and cardiac competency. Another serious cause of poor return is the excessive use of positive-pressure respirators.

Acute Cardiac Failure

The aged person is quite susceptible to acute cardiac failure, particularly if he already has valvular disease or hypertension. The dangers of acute failure peculiar to each type of valve deformity are well known. Perhaps it would be appropriate here to emphasize once more that very close attention to the patient's water and salt requirements is necessary.

In evaluating the cardiovascular complications in cases of surgery of the chest there is a very special problem that I should like to discuss briefly:

The use of digitalis in the operative and postoperative period should be limited, I believe, to cases having clear evidence of cardiac failure, as revealed by signs of cardiac enlargement and congestion in the pulmonary or systemic venous circuits. In chest-surgery cases the patient may have marked tachypnea, dyspnea due to spasm, pain, shift of the mediastinum, and elevation of the diaphragm with partial collapse of a lung or compression by fluid. The pulse may be rapid. There may be cyanosis. In such cases, the operation probably has caused some serous pleural or mediastinal pericarditis. The heart and great vessels may be shifted. Some of these signs may be mistakenly ascribed to cardiac failure. The use of digitalis without clear-cut evidence of cardiac failure may lead to more circulatory embarrassment by bringing on auricular flutter, fibrillation, or ventricular ectopic foci, all of which are frequent enough in this type of case.

Coronary Disease

The complications of coronary insufficiency and myocardial infarction are very difficult to evaluate. The internist always feels considerable anxiety when an aged patient with coronary insufficiency or with a previous myocardial infarction undergoes anesthesia. I am impressed by the ease with which the anesthesiologist carries most of such patients through operation. Particular attention is paid to the avoidance of undue physical

and mental stress, to adequacy of the blood volume, to oxygen supply, and to maintenance of steady, smooth arterial blood pressure. The aortic diastolic blood pressure is the perfusion pressure of the coronary system. Patients with aortic insufficiency present perhaps the most striking examples of a dangerously low diastolic coronary perfusion pressure. If there is, in addition, some narrowing of the coronary ostia, an aortic pressure drop may be fatal.

Older hypotensive patients frequently present us with the problem of deciding how low a previously abnormally high pressure should be allowed to drop. Ought we to start treating the blood pressure sooner than we would in the younger normotensive patient whose pressure is falling? This is a problem the internist often faces in older patients who become hypotensive following a myocardial infarction. Some of us, I believe, fall into the habit of treating the blood pressure without reference to its previous level. For the aged patient and the patient with coronary disease, the regulation of blood pressure is most important. The use of pressure-maintaining drugs, such as norepinephrine, has greatly improved the outlook for cases of myocardial infarction with hypotension.

Abnormalities of Adrenal Function, and of Water, Sodium, Potassium, and Protein Metabolism

There is increasing evidence that in some patients the stress of operation may reveal the inadequacy of their adrenal function. This deficiency is revealed by lowered blood pressure, a failure to excrete water, and a low concentration of sodium and chloride in the body fluids. It should be remembered, however, that a similar picture can be produced by the excessive administration of water to any patient. A particularly striking example of the misuse of water is the circulatory embarrassment and, occasionally, shock that may occur when water is given by hypodermoclysis. A solution of 5 per cent dextrose in water, administered subcutaneously, may be poorly absorbed. Sodium and chloride from plasma then diffuse into the water. This causes a fall in plasma volume, a lowered cardiac output, and a decreased peripheral circulation. The serum sodium and chloride concentration fall. The oliguria that may occur in the operative and postoperative period tends to accentuate this water intoxication.

Lowered blood volumes can also result from deficiency of plasma proteins due to leakage from inflamed, burned, or damaged surfaces.

Finally, in evaluating cardiovascular complications, it should be mentioned that a deficiency of potassium may cause neuromuscular and cardiac weakness, with lowered blood pressure and peripheral circulatory insufficiency. A patient with low potassium may also be much more susceptible to the development of arrhythmias in the presence of digitalis. Patients who have had vomiting, intestinal drainage, diarrhea, or enemas, or who have been using cathartics excessively, may be potassium-deficient. Electrocardiography is a very valuable clinical method for assessing potassium

deficiency. Chemical determination of the serum will usually reveal a low concentration; however, the total body deficit may be large with a serum level which is not strikingly low.

On the other hand, a high serum potassium level will also cause depression of cardiac activity. This is most likely to occur in patients with renal insufficiency. Again, the electrocardiographic picture and the serum chemical determination are important.

Reference

1. Briggs, B. D., D. B. Sheldon & H. K. Beecher. 1956. Cardiac arrest. Study of a thirty-one year period of operating room deaths at Massachusetts General Hospital 1925–1954. J. Am. Med. Assoc. **160**: 1439.

THE USE OF MECHANICAL RESPIRATORS IN PATIENTS WITH A HIGH AIRWAY RESISTANCE*

By J. B. Hickam, H. O. Sieker, W. W. Pryor, and R. Frayser
Department of Medicine, Duke University School of Medicine, Durham, N. C.

In the last few years mechanical respirators have been used widely in the treatment of carbon dioxide narcosis.[1-4] This condition is prone to develop in persons with disorders such as pulmonary emphysema, in which alveolar ventilation is reduced.[5, 6] The basic disorder is usually accompanied by some acute, reversible complication such as pulmonary infection, heart failure, or oversedation that has precipitated ventilatory failure and necessitated oxygen therapy. The object of using a respirator is to maintain adequate alveolar ventilation until treatment of the reversible component of the illness enables the patient to continue without further assistance.

Such patients present formidable obstacles to the successful use of a respirator. The over-all airway resistance is usually quite high, and the pulmonary compliance is low. The problem is to provide adequate ventilation without damaging the lung by excessive pressures.

It is the purpose of this paper to outline in quantitative terms the mechanical problems involved in using a respirator on a patient with high resistance and low compliance and to show what performance characteristics of the respirator are desirable for use on such a patient.

Methods

I shall begin by describing a simplified patient-respirator system that includes the major variables, and by analyzing the behavior of this system. This analysis will emphasize the factors that are important for successful operation of the simplified system against a high airway resistance. I shall then discuss the validation of these results in the use of an actual respirator on a simulated lung and by reference to experience with the use of the respirator on patients.

The Seeler respirator[7] was used as the model for this study. This is a pneumatic-balance-type respirator that inflates the lungs until a preset positive pressure is attained. The respirator then cycles automatically and deflates the lungs until a preset negative pressure is attained, after which the cycle is repeated. Negative pressure is obtained by a venturi effect. The respirator is actuated by compressed gas delivered to the patient by way of a tight-fitting face mask or a tracheal airway. Control over respirator function is provided by 3 variables that can be adjusted independently. These are: line pressure, inflow resistance, and mask-pressure range. Line pressure is the pressure at which gas is supplied to the respirator from the source. The range used in this study was from 20 to 90 cm.

* The work described in this paper was supported by a research grant [Public Health Service H-1370 (C-3)] from the National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

H_2O. Inflow resistance is provided by a variable orifice interposed between the supply line and the respirator proper. Inflow resistance can be varied continuously between 85 and 650 cm. $H_2O/(l./sec.)^2$. Mask-pressure range is the difference between the positive and negative pressures at which the valve cycles. This can be varied from 8 to 30 cm. H_2O.

The variables in the patient that were taken into account were compliance and airway resistance. Compliance is an expression of the elastic properties of the lung and chest wall and is measured as change in volume of the lungs and thorax per unit pressure change. The normal value is taken to be 1000 ml./14.7 cm. H_2O. Resistance refers to the pressure required to maintain gas flow through the airways. Normally, this is 1 to 2 cm. H_2O at a flow rate of 1 liter per second.

Simplifying assumptions as to the behavior of the patient-respirator system have been made, and expressions have been derived to describe the functioning of this system within the limits of the assumptions.[8] The essential features of the assumptions and derivation are presented in the Appendix to this paper.

Simulated lungs[9] consisted of bottles with capacities of 70, 41, and 20.5 liters, which provided respective pressure changes of 14.7, 25, and 50 cm. H_2O/liter at a barometric pressure of 755 mm. Hg. Any desired resistance could be obtained by interposing a constriction in the tubing between the respirator and the bottle. Resistances of 3.5 and 64 cm. $H_2O/(l./sec.)^2$ were used to represent nearly normal and greatly increased airway resistances. When connected with such a simulated lung, the respirator cycled automatically. Line pressure, mask pressure, and the pressure difference across a wire screen flowmeter were measured with strain gauges and recorded on an oscillograph. Tidal volume was obtained from the area under the flow tracing. When observations were made on an actual patient, the resistance and compliance of the patient were estimated from the recordings by Radford's method,[10] modified to conform with the assumption $P = k\dot{V}^2$ (see Appendix).

Results

Respirator Function in a Subject with Normal Pulmonary Mechanics

Figure 1 shows how the total calculated minute ventilation delivered by the respirator to a normal subject varies with change in the respirator variables. Decreasing the inflow resistance or raising the line pressure increases total ventilation. However, change in mask-pressure range has little effect, because the change in tidal volume that results from altering mask pressure is almost exactly balanced by an inverse change in the cycling rate. For the same reason, total minute ventilation is very nearly independent of the compliance of the subject, but increasing the resistance of the subject will decrease total ventilation.

All of the patient and respirator variables significantly influence the

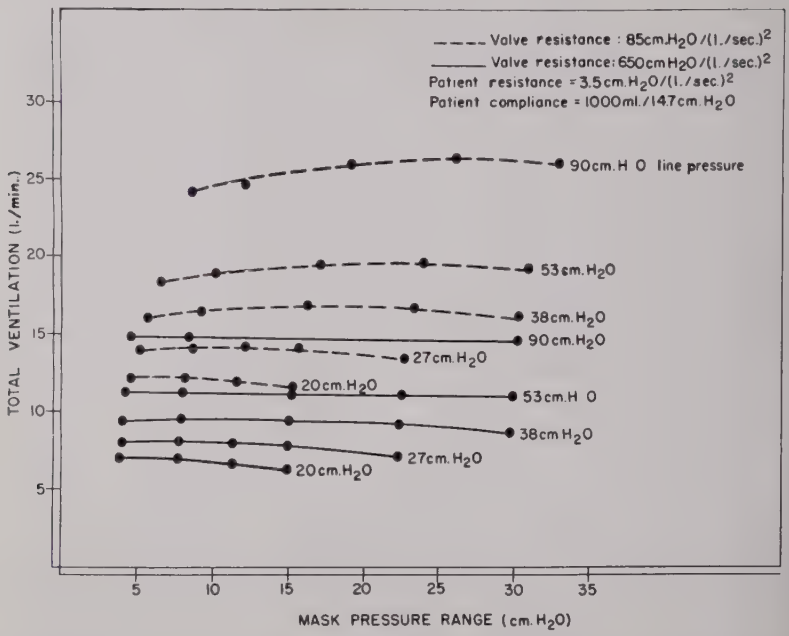

FIGURE 1. Calculated total minute ventilation provided to a hypothetical normal subject by the Seeler respirator at different settings of the respirator controls. Increasing the line pressure or decreasing the valve resistance increases ventilation, but changing the mask-pressure range has little effect.

"effective ventilation rate," which is the total minute ventilation less dead-space ventilation. FIGURE 2 shows the dependence of effective ventilation on mask-pressure range at a variety of line pressures. Effective ventilation is dependent on the compliance as well as the resistance of the subject.

It is apparent that the respirator is capable of providing a wide range of effective ventilation rates to a normal subject. Adequate ventilation can be provided at a low mask-pressure range.

FIGURE 3 shows that the total ventilation rate obtained with the actual respirator and a simulated normal lung varied much as predicted with change in line pressure and mask-pressure range.

Respirator Function in a Subject with High Resistance and Normal to Low Compliance

Mask-pressure range. The effect of increasing patient resistance and decreasing compliance is to reduce the rate at which gas can be delivered to the patient and to reduce the tidal volume that can be achieved within the limits of a given mask-pressure range. In consequence, the effective ventila-

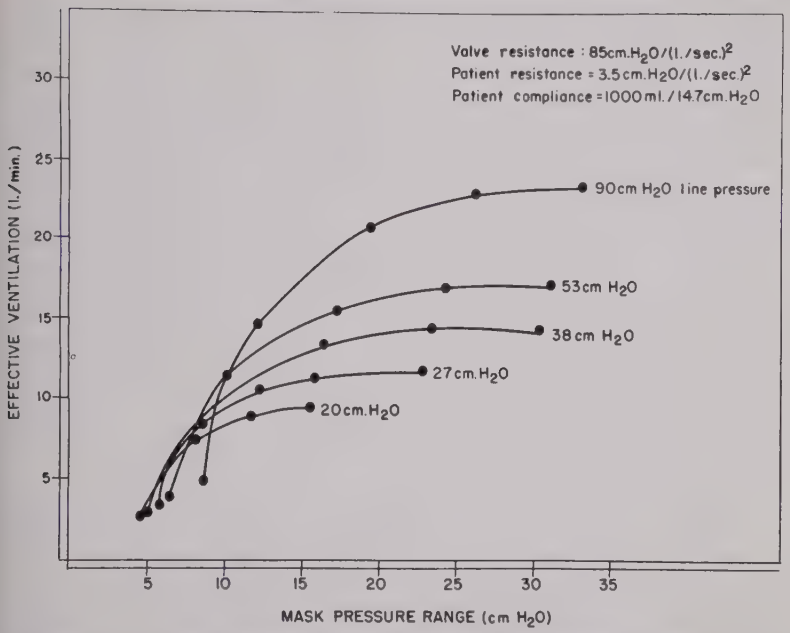

FIGURE 2. Calculated effective ventilation provided to a hypothetical normal subject by the Seeler respirator. The valve resistance is fixed at a low value, but the line pressure and the mask-pressure range are allowed to vary. Effective ventilation is total ventilation less dead-space ventilation. Effective ventilation is dependent upon mask-pressure range as well as upon line pressure and valve resistance.

tion rate is reduced. In this situation, increasing the mask-pressure range will increase effective ventilation again because it makes more pressure available for moving gas through the narrowed airways and distending the stiffened lung. For this reason, when airway resistance is very high, it is advantageous to use as high a mask-pressure range as is compatible with safety. For the present analysis, a mask-pressure range of 30 cm. H_2O was selected.

Line pressure and inflow resistance of the respirator. For the present purpose, altering the line pressure and changing the respirator resistance have much the same effect: to change the rate at which gas is delivered into the mask during inspiration. Increasing this rate by raising the line pressure or lowering the resistance tends to increase total minute ventilation. However, in a patient with high airway resistance, effective ventilation may simultaneously be reduced because the tidal volume falls off rapidly with an increase in the inflow rate. This is because so much of the available mask pressure is needed to maintain a high rate of flow of gas into the patient that little is left for overcoming elastic resistance and

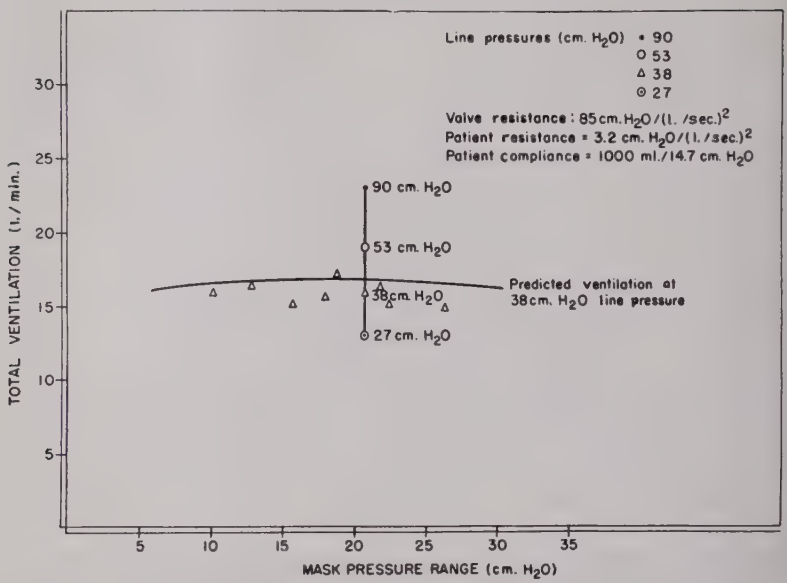

FIGURE 3. Actual values of minute ventilation obtained with the use of the Seeler respirator on a simulated lung. Ventilation rates with a line pressure of 38 cm. H_2O are close to the predicted values, indicated by the curved horizontal line. Variation in mask-pressure range at a given line pressure has no significant effect on the total ventilation. Varying the line pressure at a constant mask-pressure range changes ventilation markedly.

distending the lung. The situation can be clarified by using EQUATION 8 of the APPENDIX to demonstrate the relation between the upper limit of mask pressure during inspiration P_{mi}, line pressure P_o, inflow resistance of the respirator k_i, patient elastance A, tidal volume Q_o, and patient resistance k:

$$P_{mi} = \frac{k_i Q_o A}{k_i + k} + \frac{k P_o}{k_i + k}$$

The second term on the right is equal to P_{ii}, the mask pressure developed immediately at the onset of inspiration (see EQUATION 7). Increasing line pressure, P_o, or reducing inflow resistance, k_i, will increase P_{ii}, and, at a fixed value of P_{mi}, will necessitate a decrease in the first term on the right and, in particular, in Q_o, the tidal volume. As Q_o approaches the dead-space volume, the effective ventilation will approach zero.

These considerations suggest that increasing the rate at which the respirator delivers gas to the patient will increase effective ventilation when the inflow rate is relatively low, but will decrease effective ventilation when the inflow rate is relatively high. Moreover, it should be possible, in a particular case, to find an intermediate inflow rate that would provide the

maximum possible effective ventilation within the given operating conditions. With the respirator used in this study, inflow rate may be varied by changing either line pressure or inspiratory resistance, and the effect can easily be examined by using the calculations of the APPENDIX. FIGURE 4 shows the calculated effect of changing line pressure on ventilation while the respirator resistance is held constant for a patient with a high airway resistance. In this case, effective ventilation is greatest at a line pressure of about 35 cm. H_2O and begins to fall off rapidly above 40 or below 30 cm. H_2O. FIGURE 5 presents the result of changing the respirator resistance while the line pressure is held constant near the usual operating level for this respirator. The solid lines show the calculated effective ventilation provided to 3 hypothetical patients having the same high airway resistance, but different compliances. The calculated total ventilation is nearly the same for all 3, but it is evident that decreasing the compliance (increasing "elastance") progressively reduces effective ventilation. Also presented in FIGURE 5 are experimental data obtained by using the actual respirator on simulated lungs having the resistance and compliance of the two most severe cases. There is sufficient agreement between the trend of calculated and experimental results in the specific cases to lend some support to the use of the calculation procedure in exploring this general problem. FIGURE 5 indicates that it is possible to find an optimal resistance setting in these cases although, in the case with the lowest compliance, the

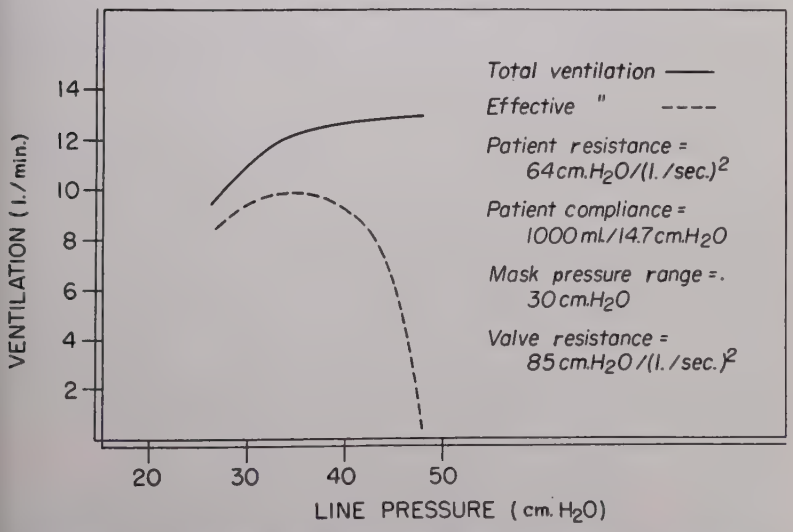

FIGURE 4. The calculated effect on total and effective ventilation of changing line pressure when the resistance of the patient is high. Respirator resistance is held constant at a low value. Effective ventilation is maximal at a line pressure of about 35 cm. H_2O.

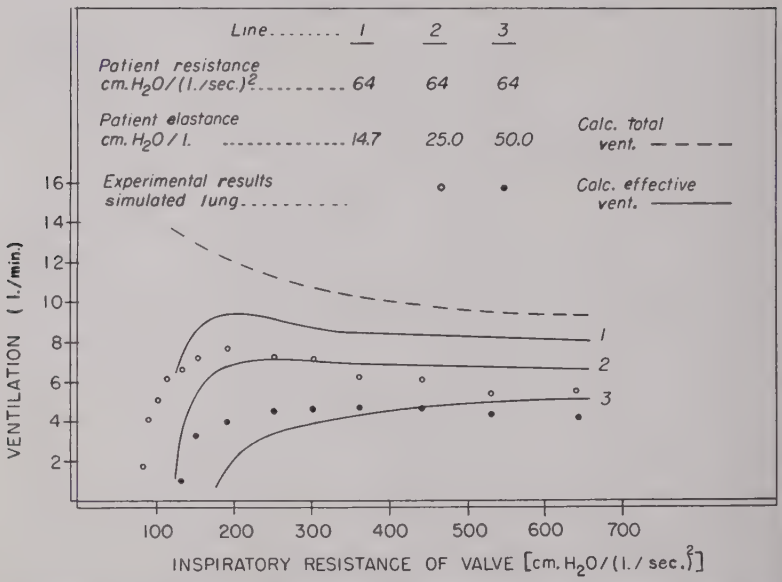

FIGURE 5. The effect on ventilation of changing the valve resistance when the patient resistance is high and the compliance is low. The line pressure is held constant at 53 cm. H_2O and the mask-pressure range at 30 cm. H_2O. The solid and broken lines indicate calculated ventilation. The points show experimental results obtained with the use of the respirator on simulated lungs having the characteristics of the hypothetical lungs corresponding to lines 2 and 3. The need for using a high valve resistance on such patients is evident.

optimal resistance is greater than can be provided by this particular respirator. Once the maximal effective ventilation has been attained by progressively increasing the respirator resistance from its lowest value, the effective ventilation is not very sensitive to further increases in resistance.

These results bear out the prediction that progressively increasing the inflow rate will first cause effective ventilation to increase, then to pass through a maximal value, and finally to decline toward zero. A similar finding was obtained by Radford for the "general low-pressure valve."[14] In the calculated examples of FIGURE 5, the maximal effective minute ventilation rates occurred at relatively slow inflow rates. The peak inflow rates at maximal effective ventilation were, for cases 1, 2, and 3, respectively, 27, 23, and 16 l./min.

Comparison of Actual with Predicted Performance of the Respirator in a Patient with Moderately Increased Resistance and Decreased Compliance

The patient was a 58-year-old male who had suffered a cerebral vascular accident and was unconscious and almost apneic. A tracheal airway was

used. The resistance was estimated at end-inspiration to be 21 cm. $H_2O/(l./sec.)^2$, and to be 46 cm. $H_2O/(l./sec.)^2$ at end-expiration. The effective resistance was taken to be the mean of these, or 33 cm. $H_2O/(l./sec.)^2$. Compliance was estimated to be 1000 ml./35 cm. H_2O. Table 1 shows a comparison between the predicted and actual performance of the Seeler respirator in this patient at several different settings of the respirator variables. It is apparent that there is a general correspondence between "actual" and "predicted" values in terms of over-all trends, although the actual numerical correspondence is erratic.

Discussion

The important qualitative results of this study could have been predicted from general principles without actually performing any calculations: to provide effective ventilation to a patient with high resistance and low compliance, it is advantageous to choose as high a mask-pressure range as is compatible with safety. When this has been done, the inflow rate of gas should be adjusted to the vicinity of the optimal value for the case at hand: too high or too low an inflow rate can reduce effective ventilation below adequate levels. The important quantitative results of the study could not have been predicted easily without the calculations. The general correspondence between the results predicted by calculation and those actually obtained by using the respirator on model lungs and on a patient support, essentially, the validity of the quantitative results.

Optimal inflow rates for patients with severe obstructive respiratory disorders are quite low. In the present examples, optimal peak inspiratory flows were in the range of 15 to 30 liters/min. and, if more severe conditions had been considered, still lower flow rates would have been desirable. This finding has an important practical application in guiding the selection of a respirator for patients of this kind. In such cases it should be possible

Table 1

Comparison of Theoretically Predicted with Actual Ventilation Provided by Seeler Resuscitator

Patient resistance, 33 cm. H_2O $(l./sec.)^2$; compliance, 1000 ml./35 cm. H_2O

	Line pressure (cm. H_2O)	Inspiratory resistance (cm. $H_2O/(l./sec.)^2$)	Mask-pressure range (cm. H_2O)	Tidal volume (liters)	Insp. time (sec.)	Exp. time (sec.)	Resp. rate (cycles/min.)	Total vent. (l./min.)	Effective ventilation (l./min.)
Predicted	53	85	32.4	0.460	0.74	0.86	37.5	17.2	9.6
Actual	53	85	32.4	0.430	0.85	0.96	33.3	14.2	7.7
Predicted	27	85	17.2	0.264	0.60	0.72	45.4	12.0	2.9
Actual	27	85	17.2	0.183	0.55	0.56	54.0	9.9	0.0
Predicted	24	650	15.3	0.390	2.40	1.08	17.1	6.7	3.3
Actual	24	650	15.3	0.210	1.37	0.67	29.4	6.2	0.3

to regulate the inflow rate of gas over a wide range and down to much slower rates than are usually available. For example, some of the better-known intermittent positive-pressure devices commercially available are occasionally used to assist breathing in patients with incipient or established carbon dioxide narcosis. Although useful in other applications, they are generally not very effective in these patients because, at the necessary mask-pressure ranges, they provide peak flow rates in the neighborhood of 80 to 90 liters/min. In our hands they have been far less effective than the Seeler respirator in reducing the arterial CO_2 tension of patients with severe obstructive disease. In general, tank respirators also fail to provide the most advantageous combination of a high mask-pressure range and a slow, sustained rate of inflow, although they often can supply adequate ventilation for these patients.

In patients with a high airway resistance, the use of a slow inflow rate has the additional advantage over a fast rate in that it provides more uniform gas distribution to the lungs and increases the apparent compliance,[11, 12] with a consequent tendency to increase effective ventilation.

Although this analysis does not take into account absolute mask pressures, but only the pressure range, in actual practice a given pressure range will tend to provide better ventilation when the absolute values are high than when they are low or partially negative. This is due, at least in part, to a reduction of airway resistance on distending the lung. The ventilatory advantages of high absolute mask pressures may be offset by their deleterious effect on the circulation.

The safe upper limit of positive mask pressure is not well-established. For normal persons, the Dill Committee suggested 37 cm. H_2O.[13] Patients with chronic obstructive pulmonary disease often have, on the surface of their lungs, thin-walled cysts that may communicate with airways having a relatively low inspiratory resistance. Such cysts occasionally rupture spontaneously, and they might easily be broken by a high positive pressure. At present, we do not exceed positive pressures of 30 cm. H_2O in any patient, and it is usually possible to achieve adequate ventilation in patients with carbon dioxide narcosis by the use of much lower maximum pressures.[8]

Summary

(1) This study outlines the mechanical problems involved in using pressure-cycled respirators on patients with high airway resistance and low pulmonary compliance.

(2) For use on such patients a respirator should be able to provide: (a) a wide mask-pressure range with a maximum positive pressure of about 30 cm. H_2O; and (b) wide variability in the rate at which gas is supplied to the patient, with the capability of reducing the peak inflow rate to approximately 10 liters per minute.

Appendix

Theoretical Study of the Operation of the Seeler Respirator

Assumptions. The first three assumptions are identical with those made in a previous analysis by Radford.[14] The assumptions are as follows:

(1) The line pressure is constant.

(2) In terms of resistance and compliance, the subject functions as a single system; that is, there is only one compliance and one resistance within the system. This assumption is certainly inexact for persons with a high airway resistance.[12]

(3) Compliance and resistance are constant during the cycle. Actually, they both alter with change in lung volume and with direction of gas flow.[14, 15] In particular, resistance increases as the lung volume decreases and, at a given volume, it is greater during expiration than during inspiration.

(4) Pressure-flow relationships for both patient and respirator are such that $P = k\dot{V}^2$, where P is the pressure responsible for a flow of gas, $\dot{V}$ is the rate of flow, and k is a constant, the "resistance." This expression fits the behavior of the Seeler respirator and the high resistances used in the present simulated lung. Our preliminary results suggest that it also applies better to patients with a very high airway resistance than does the linear expression, $P = k\dot{V}$, which applies well to normal subjects.[14] Actually, when the resistance is normally low, there is very little difference between the results obtained with the two expressions under the circumstances of this study.

(5) A simple approximation with an empirical basis is used to describe the expiratory behavior of the respirator. Expiratory pressure-flow relationships are taken to obey the expression

$$P_m - aP_o = k_e\dot{V}^2$$

where P_m is mask pressure; $\dot{V}$ is flow rate; k_e, the "expiratory resistance" of the respirator, is a constant; P_o is line pressure, and a is a constant. Both a and k_e are approximately constant at a given inspiratory resistance setting of the respirator. The expression aP_o is the effective venturi pressure that assists expiration. When the inspiratory respirator resistance, k_i, is 85 cm. $H_2O/(l./sec.)^2$, k_e is 64 cm. $H_2O/(l./sec.)^2$ and a is -0.33; when k_i is 650 cm. $H_2O/(l./sec.)^2$, k_e is 27 cm. $H_2O/(l./sec.)^2$ and a is -0.10.

Symbols and Conditions. Let Q = volume of gas in liters (ATPS) added to the lung during the inspiratory portion of the cycle. No allowance is made for change in temperature or water-vapor content as the gas is passed from the source, through the respirator, and into the lung.

A = elastance (1/compliance) of lung and chest wall in cm. H_2O/liter.

P_p = the intrapulmonary gas pressure in cm. H_2O owing to elastance of the lung and chest wall. When $Q = 0$, $P_p = 0$. At other values of Q, $P_p = QA$.

P_o = line pressure (cm. H_2O), or pressure at which gas is supplied from the source to the respirator.

P_m = mask pressure in cm. H_2O.

P_{mi} and P_{mx} are the mask pressures at which inspiration and expiration, respectively, are interrupted by the cycling of the respirator. $P_{mi} - P_{mx}$ is the mask-pressure range.

P_{ii} and P_{ix} are the initial mask pressures at the start of inspiration and expiration, respectively. Mask pressure is discontinuous at the point where the respirator cycles. At the beginning of inspiration, mask pressure passes discontinuously from P_{mx} to P_{ii}. At the end of inspiration, mask pressure passes discontinuously from P_{mi} to P_{ix} to start expiration.

k_i and k_e are the inspiratory and expiratory respirator resistances in cm. $H_2O/(l./sec.)^2$.

k = the patient resistance in cm. $H_2O/(l./sec.)^2$.

t_i = duration of inspiration in sec.

t_x = duration of expiration in sec.

F = respiratory rate in cycles/min.

$\dot{V}$ = ventilation rate in l./min. (ATPS). For calculating "effective" ventilation rate, a dead space of 200 ml. is postulated. Effective ventilation rate = $\dot{V} - 0.200\ F$, in l./min.

aP_o = effective venturi pressure in cm. H_2O.

For simplicity, the condition is imposed that expiration end at the relaxation volume of the lung ($Q = 0$).

The Basic Equations

$$P_p = QA \tag{1}$$

For inflow through the respirator:

$$\left(\frac{dQ}{dt}\right)^2 k_i = P_o - P_m \tag{2}$$

For inflow into the patient:

$$\left(\frac{dQ}{dt}\right)^2 k = P_m - QA \tag{3}$$

For outflow from the patient:

$$\left(\frac{dQ}{dt}\right)^2 k = QA - P_m \tag{4}$$

For outflow through the respirator:

$$\left(\frac{dQ}{dt}\right)^2 k_e = P_m - aP_o \tag{5}$$

Applicable Solutions

For inspiration

Q

$$Q = \frac{k_i + k}{Ak_i} P_m - \frac{kP_o}{Ak_i} \tag{6}$$

P_{ii} When $Q = 0$,

$$P_m = P_{ii} = \frac{kP_o}{k_i + k} \tag{7}$$

P_{mi} At end-inspiration, when $Q = Q_o$,

$$P_{mi} = \frac{k_i Q_o A}{k_i + k} + \frac{kP_o}{k_i + k} \tag{8}$$

t_i

$$t_i = \frac{2(k_i + k)}{Ak_i^2}\left(\sqrt{P_o - P_{ii}} - \sqrt{P_o - P_{mi}}\right) \tag{9}$$

For expiration

Q

$$Q = \frac{k_e + k}{Ak_e} P_m - \frac{k}{Ak_e} aP_o \tag{10}$$

P_{ix}

$$P_{ix} = \frac{Ak_e}{k_e + k} Q_o + \frac{k}{k_e + k} aP_o \tag{11}$$

P_{mx}

$$P_{mx} = \frac{k}{k_e + k} aP_o \tag{12}$$

t_x

$$t_x = \frac{2(k_e + k)}{Ak_e^2}\left(\sqrt{P_{ix} - aP_o} - \sqrt{P_{mx} - aP_o}\right) \tag{13}$$

The equations presented immediately above allow description of a complete cycle of the respirator within the limitations previously discussed. P_o, A, k, k_e, and k_i are given. In actual practice, the mask-pressure range is varied as desired, and Q_o, the tidal volume, is thereby determined. As the present analysis is set up, Q_o is chosen, and this determines the cycling pressures. Other variables such as cycling time, total minute ventilation, effective minute ventilation, and flow rates are also dependent variables, and their values can be determined from the equations.

To calculate the effect on ventilation of changing valve resistance alone, it is necessary to make some approximations to cover the expiratory behavior of the respirator at inspiratory respirator resistances (k_i) between the two extremes of 85 and 650 cm. H_2O (l./sec.)^2, for which the behavior is known from experimental trials. The mask pressure at the end of expiration (P_{mx}) is given by EQUATION 12. At the high patient resistances considered in this study, P_{mx} is about -8 cm. H_2O at the low limit of k_i and -4 cm. H_2O at the high limit of k_i. The assumption is made that there is a linear relationship between k_i and P_{mx} in the interval between these two limits of inspiratory respirator resistance. This assumption appears to introduce little error. P_{mi}, the mask pressure at the end of inspiration, is next obtained from the relation

$$P_{mi} = 30 + P_{mx}$$

since a pressure range of 30 cm. H_2O has been postulated. Q_v is now obtained from EQUATION 8, P_{ti} from (7), and t_i from (9). To obtain t_x, the further assumption is made that a linear relationship holds between the ratio t_x/t_i and k_i in the interval between the limits of k_i. This allows calculation of the total cycling time. Where the assumed resistance of the patient was so high that the valve would not cycle at a k_i of 85 cm. $H_2O/(l./sec.)^2$, calculations were based on the approximation that $a = -0.33$ and $k_e = 64$ cm. $H_2O/(l./sec.)^2$ at a k_i of 100 cm. $H_2O/(l./sec.)^2$.

Actual trials with the model lung indicate that these approximations yield a somewhat greater value for t_x/t_i than actually occurs. The largest discrepancy, which occurs near a k_i of 200, amounts to an excess of about 25 per cent over the true value. The result is in the direction of underestimating the effective ventilation that the respirator delivers at low values of k_i to a patient with a high airway resistance.

References

1. BOUTOURLINE-YOUNG, H. J. & J. L. WHITTENBERGER. 1951. The use of artificial respiration in pulmonary emphysema accompanied by high carbon dioxide levels. J. Clin. Invest. **30:** 838.
2. LOVEJOY, F. W., JR., P. N. G. YU, R. E. NYE, JR., H. A. JOOS & J. H. SIMPSON. 1954. Pulmonary hypertension. III. Physiologic studies in three cases of carbon dioxide narcosis treated by artificial respiration. Am. J. Med. **16:** 4.
3. KAPLAN, E., J. DETWEILER, B. M. KAPLAN & L. A. BAKER. 1954. Respirator in chronic pulmonary disease with spondylitis and fixation of thorax. J. Am. Med. Assoc. **156:** 1499.
4. SIEKER, H. O., J. B. HICKAM & W. W. PRYOR. 1956. The treatment of carbon dioxide narcosis by the use of an automatic positive-negative resuscitator. Am. Rev. Tuber. & Pulmonary Disease. **74:** 309.
5. COMROE, J. H., JR., E. R. BAHNSON & E. O. COATES, JR. 1950. Mental changes occurring in chronically anoxemic patients during oxygen therapy. J. Am. Med. Assoc. **143:** 1044.
6. WEST, J. R., E. D. BALDWIN, A. COURNAND & D. W. RICHARDS, JR. 1951. Physiopathologic aspects of chronic pulmonary emphysema. Am. J. Med. **10:** 481.
7. SEELER, H. W. & D. R. GOOD. 1953. Automatic resuscitator. J. Aviation Med. **24:** 63.
8. HICKAM, J. B., H. O. SIEKER, W. W. PRYOR & R. FRAYSER. 1955. Use of the Seeler resuscitator in man. WADC Tech. Rept. 55–165. Wright-Patterson Air Force Base. Dayton, Ohio.
9. FENN, W. O., A. B. OTIS & H. RAHN. 1945. Mechanical behavior of the Burns pneumatic balance resuscitator. *In* Studies in Respiratory Physiology. 1951. AF Tech. Rept. No. 6528. WADC. Wright-Patterson Air Force Base. Dayton, Ohio.
10. RADFORD, E. P. 1953. Method of obtaining data relating to the mechanical properties of lungs, chest, and airway of patients given artificial respiration with a pressure-cycled resuscitator. Chem. Corps Med. Lab. Special Rept. No. 28. Army Chemical Center, Md.
11. MEAD, J., I. LINDGREN & E. A. GAENSLER. 1955. The mechanical properties of the lungs in emphysema. J. Clin. Invest. **34:** 1005.

12. Otis, A. B., C. B. McKerrow, R. A. Bartlett, J. Mead, M. B. McIlroy, N. J. Selverstone & E. P. Radford. 1956. Mechanical factors in distribution of pulmonary ventilation. J. Appl. Physiol. **8**: 427.
13. Chemical Corps Medical Laboratories Special Report No. 38. 1954. Army Chemical Center, Md.
14. Radford, E. P. 1953. The engineering of mask respirators from the physiologic point of view. Chem. Corps Med. Lab. Special Rept. No. 19. Army Chemical Center, Md.
15. Otis, A. B., W. O. Fenn & H. Rahn. 1950. Mechanics of breathing in man. J. Appl. Physiol. **2**: 592.

CHOICE OF ANESTHESIA FOR GERIATRIC PATIENTS

By C. R. Stephen

Division of Anesthesia, Duke University Hospital and School of Medicine, Durham, N. C.

"Any anesthetic or method, or combination of anesthetics and methods, that is serviceable and good at all, is serviceable and good for old people. The main difference is that these people are tender, are quieted easily with sedatives, are anesthetized and relaxed easily and overdosed readily. What they require particularly is conservatism with a little daring mixed in, but with unceasing vigilance and nicety and exactness of administration and control."[1] In this way Ralph Knight has epitomized our approach to the geriatric patient.

One of the things that the teacher in anesthesia learns over a period of time is the extent of physiological insult to which the average healthy adult can on occasion be exposed during operation without irreparable damage to vital organs. The patient can survive hypoxia, hypercapnia, hypotension, deep planes of anesthesia, and traumatic surgery for hours at a time, and still be alert and active the following day.

Patients in the older age group fall into a different category of anesthetic management. Their shell of natural resistance is infiltrated more easily; their armor of tolerance for physiological aberrations is thin and patchy. In short, the allowable error in anesthetic administration is reduced to a narrow range.

Why do advancing years increase the hazard of surgical interference? One of the factors involved is the loss of elasticity in tissues that develops with the natural process of aging.[2] This lack of resiliency is reflected particularly in the respiratory, cardiovascular, and renal systems. Manifestations in the respiratory system appear as pulmonary fibrosis and as emphysema. When such changes are present, pulmonary gas mixing becomes more difficult, and the alveolar exchange of oxygen and carbon dioxide is handicapped. Pulmonary reserve is reduced, and the allowable margin of error in tidal exchange and in minute volume respiration during anesthesia is narrowed.

In its indirect manifestations on the heart and in its local, direct effects on the cerebral, coronary, and renal vessels, loss of elasticity in the vascular system is of particular importance to the anesthesiologist. In time, generalized hypertensive arteriosclerotic disease increases the work load of the heart, increases the size of this organ, and gradually decreases its efficiency as a pump. Its latent reserve of muscular power is drawn into action, so that little remains to combat effectively the extra stresses that may be precipitated by sudden episodes of hypoxia, hypercapnia, or deep anesthesia.

With an increased work load on the heart, the functioning of the coronary vessels may become relatively inadequate. If they also become involved in

the generalized atherosclerotic process, the prevention of acute myocardial ischemia becomes a major problem. The importance of maintaining the mean arterial pressure during anesthesia is obvious, and the avoidance of extra strain on the heart becomes mandatory.

Similarly, if the cerebral vessels are deficient in elasticity and are sclerotic, the importance of adequate arterial oxygenation and blood flow to the brain cannot be overemphasized. It is of interest to note the recent report of Bedford,[3] which indicates that periods of general anesthesia in the elderly may be followed by permanent irreversible dementia. Bedford stresses the importance of avoiding cerebral circulatory failure and its associated anoxia during operative procedures.

It is known that in most types of general anesthesia renal function is depressed, the degree of depression depending to some extent on the depth as well as the length of anesthesia.[4] When renal insufficiency already exists in the geriatric patient, the feasibility of regional forms of analgesia is worth exploring.

Another factor of importance in the older patient, probably related to the loss of vessel elasticity associated with age, is the danger of thrombosis or embolism during or after operation. In a recent series of 605 geriatric operations it was found that the commonest cause of postoperative mortality was thromboembolism.[5] Anesthetic management that allows hypotension to remain uncorrected or blood loss to be unreplaced may contribute to such episodes. Administration of the anesthetic in a manner that prevents rapid recovery of consciousness and physical activity may predispose the patient to vascular accidents in the postoperative period.

Physical and mental changes that occur with the natural process of aging may be described as inherent. Certain other factors, designated as acquired, may serve to increase the anesthetic risk for the geriatric patient. The particular disease process for which operation is being proposed can be a contributing menace. Gastrointestinal lesions that have reduced the appetite or prevented assimilation of food lead rapidly to weight loss, malnutrition, and decrease in blood volume. Cole states[6] that malnutrition is one of the most serious deficiencies encountered in the older patient and greatly increases the hazard of operation. Such patients are helped immeasurably by correction of blood volume deficits in the preoperative period.[7]

Apart from the specific lesion for which surgery is being done, most of the ravages of carcinoma are unknown. However, acquired anemia is a frequent concomitant of this disease, and should be corrected before the strain and stress of operation. The status of adrenocortical function in the aged is debatable at present, but recent evidence suggests that hypofunction may be present in certain instances in a degree sufficient to require adjunctive therapy during exposure to stress.[8] Other metabolic diseases, such as diabetes or pernicious anemia, may create certain problems in the choice of anesthetic drugs.

Choice of Anesthesia

Choice of anesthetic drugs and techniques ultimately depends on a careful, individual preoperative assessment of the patient. In geriatric patients, more than in any other age group, the narrow allowable margin of error dictates that each patient should be regarded as a law unto himself. Conversation with the patient allows one to estimate his degree of mental acuity and gives an indication of the amount and type of premedication required. In patients showing evidence of advanced cerebral arteriosclerosis, the possibility of avoiding general anesthesia should be entertained, because interruption of the conscious state can lead to further mental deterioration in the postoperative period.[3]

Inquiry concerning the degree of physical activity prior to hospitalization is a great aid in determining the risk to the patient. The thin, wiry, active, asthenic type is not a difficult anesthetic problem. The florid, obese, lethargic, dyspneic type is often a source of concern. The pale, gaunt, tired, cachectic individual requires most meticulous preoperative care and anesthetic management. The acutely ill emergency patient, perhaps with intestinal obstruction, a ruptured viscus, or a bleeding ulcer, needs all the art and science the anesthesiologist can muster.

Physical examination and ancillary laboratory investigations will help to evaluate the severity of the pulmonary, cardiovascular, or other changes present in the patient.

Although the anesthetic drugs and techniques employed for geriatric surgery will vary from one institution to another, certain general principles of management are applicable universally. The over-all aim is simultaneously to provide safe anesthesia and the best operating conditions for the surgeon, in order that the procedure may be completed with dispatch.

By definition, safe anesthesia is that which least disturbs the metabolic functions of the patient. When the extent and site of surgery permit, primary consideration should be given to regional techniques of pain relief. When performed with care and consideration, regional analgesia preserves mental stability and interferes less with the mode of life, and therefore the metabolic functions, than does general anesthesia.

When regional analgesia is not feasible, safe anesthesia means light planes of general anesthesia. One of the greatest errors prevalent in current anesthesia is the employment of deep planes of narcosis when these are not required. With their decreased metabolic rate and less marked reaction to painful stimuli, old people in particular are provided with adequate hypnosis and analgesia by the administration of minimal quantities of drugs. Deep planes of anesthesia are attained easily in the aged and serve to disrupt metabolic processes and prevent their early return to normalcy.

Safe general anesthesia with preservation of metabolic functions involves adequate pulmonary ventilation to ensure that oxygen reaches the blood stream freely and that carbon dioxide is eliminated properly. Such exchange can be monitored clinically by constantly watching the movements

of the patient's chest and by keeping a hand on the reservoir bag of the anesthetic gas machine. There should never be any hesitation in assisting or in controlling completely the respirations of the patient as soon as these procedures are thought to be necessary.

The second general aim of the anesthesiologist is to provide adequate operating conditions. To many surgeons this requisite primarily implies good muscular relaxation. Under general anesthesia, relaxation can be provided by deep planes of narcosis or by the use of relaxant drugs in association with light, easily reversible hypnosis and analgesia. The least risk to the geriatric patient is associated with the judicious use of muscle-relaxant drugs, assuming that the anesthetist is capable of maintaining adequate pulmonary ventilation in a proper manner at all times.

Case Presentations

The following anesthetic case histories are presented to illustrate some of the principles enumerated above:

Case 1. A 79-year-old colored male was known to have had an abdominal aneurysm for 3 years. While chopping wood, he suddenly developed acute abdominal pain, followed by unconsciousness for 30 minutes. He was immediately hospitalized. In the emergency room he was noted to be in acute distress, with dyspnea and a distended, tender abdomen. Temperature, 38°C.; blood pressure, 100/80; pulse, 130; hemoglobin, 9.0 G.; electrocardiogram, normal. The diagnosis was rupture of an abdominal aneurysm. After receiving 1500 cc. blood, which raised the hemoglobin to 12.5 G., he was brought to the operating room at 12:00 midnight, 6 hours after admission (FIGURE 1). Anesthesia was induced with surital sodium,

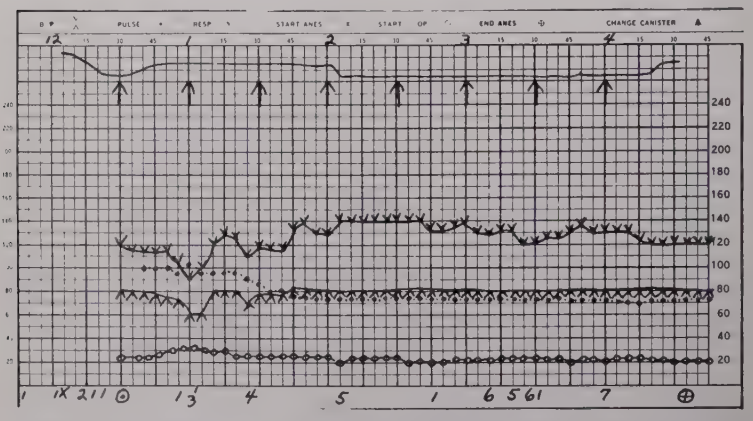

FIGURE 1. Anesthetic record of a 79-year-old patient suffering from ruptured abdominal aneurysm. Light general anesthesia was employed with succinylcholine for relaxation. Respirations were assisted or controlled throughout the operation.

60 mg., and intubation was performed with succinylcholine, 60 mg.; the larynx and trachea were cocainized at the time of intubation. Anesthesia was maintained with ethylene and oxygen, with traces of ether added as required, under assisted and controlled respirations. Relaxation was provided by succinylcholine drip, 0.1 per cent. A ruptured aneurysm of the left common iliac artery was found, and an iliac graft was inserted. Operating time was 4 hours, 15 minutes. The patient received 4000 cc. blood. Postoperatively the patient developed paralytic ileus and electrolyte imbalance. The incision dehisced on the third postoperative day and was closed under general anesthesia. Subsequently, recovery was satisfactory.

This patient represents the emergency, poor-risk type of case. Proper preparation of such patients for surgery is important. They should not be rushed immediately to the operating room on admission. Prior to operation, shock must be treated as adequately as possible. Because of the potential shock state that still existed at time of operation and the difficulty in knowing what type of surgery would be required, for this patient light general anesthesia was chosen in lieu of regional block. I should like to draw your attention to the small amount of ultra-short-acting barbiturate employed for induction. In elderly patients, even when they are not in potential shock, small quantities of these drugs exert a potent effect. Often 60 mg. in a patient 75 years old will produce as much hypnosis and depression as would 500 mg. in a patient 40 years old. Assisted and controlled respirations were maintained throughout the case to ensure adequate oxygenation and removal of carbon dioxide. The patient was awake at the end of the operation.

Case 2. An 84-year-old colored male was admitted with a history of poor appetite, loss of weight, and vomiting of blood with melena for several weeks. Severe anemia (hemoglobin of 4.5 G.) was present. X rays showed a filling defect of the stomach. The operation proposed was gastric resection. By repeated infusions of blood and serum albumin, blood volume and anemia were corrected preoperatively. Pulmonary function was believed to be adequate. Blood pressure was 180/90, the heart was enlarged, and the electrocardiogram showed evidence of left ventricular ischemia. Analgesia was obtained with a bilateral intercostal block, Th. 5 to 10 bilaterally, employing a total of 500 mg. of Xylocaine, 1.0 per cent (FIGURE 2). The hypotension that developed in association with the splanchnic block, performed under direct vision of the surgeon, was treated with a dilute intravenous drip of *levo*-arterenol. The procedure was completed satisfactorily in 2 hours. The postoperative course was satisfactory, but on the ninth day the patient had a sudden cerebral accident and died.

This patient represents the poor-risk type of patient in whom relief of pain can be achieved adequately with regional block. In such patients, it is wise to have sympathomimetic drugs immediately at hand in order to counteract loss in sympathetic tone and to aid in reversing rapidly a sudden neurogenic hypotension. A dilute solution of neosynephrin or *levo*-arterenol can be satisfactorily titrated intravenously. At the end of the operation,

FIGURE 2. Anesthetic record of an 84-year-old male, in whom a gastric resection was carried out satisfactorily with bilateral intercostal block and splanchnic block under direct vision. Analgesia was achieved with Xylocaine, 1.0 per cent, 500 mg.

methoxamine was given to prevent the possible fall in blood pressure associated with moving the patient to the recovery room.

Case 3. A 76-year-old colored male was brought to the operating room for a right colectomy and an ileotransverse colostomy to remove a carcinoma of the right colon. He suffered from moderately severe hypertensive cardiovascular disease, and had a blood pressure of 160/90. The electrocardiogram showed left ventricular ischemia. On admission his hemoglobin was 9.9 G. Preoperatively, a transfusion of 1500 cc. blood was given to correct anemia and to increase the blood volume, which was suspected to be low. Anesthesia was induced with surital sodium, 200 mg. Intubation was accomplished with succinylcholine, 60 mg. Anesthesia was maintained for 4 hours by a combination of ethylene, cyclopropane, and oxygen, using a partial rebreathing system (FIGURE 3). Muscular relaxation was provided as required by a succinylcholine drip, 0.1 per cent. Respirations were controlled throughout the procedure; blood pressure remained at "normal" levels for this patient. The postoperative course was smooth, and the patient was out of bed 24 hours following surgery.

If anemia and blood volume deficits are corrected in the preoperative period, there is less possibility that operative shock will occur. In this patient, light planes of anesthesia, accompanied by controlled respirations to maintain oxygenation and acid-base balance, allowed early awakening and activity of the patient. An active "stir-up" regimen, with minimal administration of narcotics postoperatively, reduces the frequency of thromboembolic accidents.

Case 4. An 88-year-old white female was admitted to the hospital after having fallen and fractured her hip. She was hyptertensive (B. P. 190/90), anemic (hemoglobin 9.5 G.), and had been receiving digitalis for 18 months

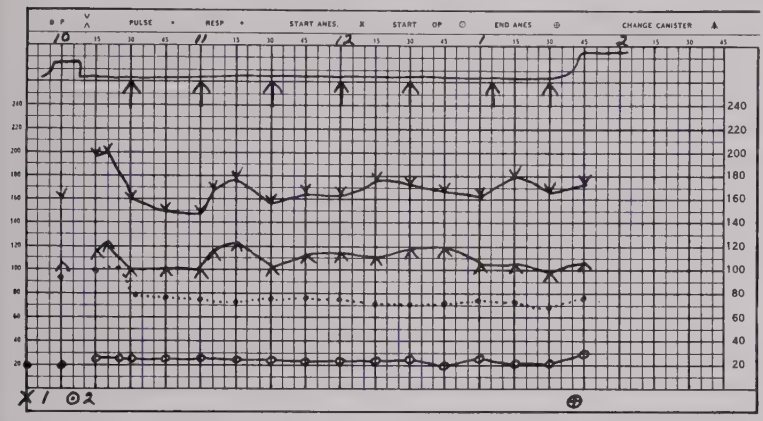

FIGURE 3. Anesthetic record of a 76-year-old male in whom a major abdominal procedure was performed under light general anesthesia with succinylcholine administered for muscular relaxation.

following an episode of cardiac failure. At the time of admission her cardiac compensation was felt to be borderline. In the last year the patient had had several episodes of disorientation and mental confusion. Her mental status was poor on admission. Preoperatively, 500 cc. of blood was administered slowly to correct anemia and blood volume. Satisfactory analgesia was induced with a unilateral hyperbaric spinal block, employing pontocaine, 8 mg., with equal parts of dextrose, 10 per cent, and spinal fluid (FIGURE 4). Ten minutes prior to subarachnoid block, ephedrine, 50 mg., was given subcutaneously and intramuscularly. Due to the patient's

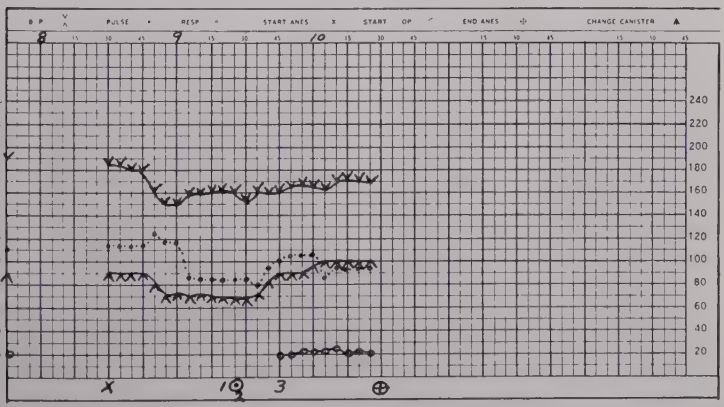

FIGURE 4. Spinal analgesia and subsequent hypnosis induced by surital and nitrous oxide disturbed metabolic function minimally in an 88-year-old female.

extreme restlessness on the operating table, unconsciousness was produced and maintained during the latter part of the procedure with surital sodium, 120 mg., and nitrous oxide and oxygen. The blood pressure remained at satisfactory levels during the operation. The postoperative progress was satisfactory. Mental confusion persisted for several days, but was not more pronounced than before the operation.

The presence of borderline cardiac failure is not a contraindication to the employment of spinal analgesia for operations on the lower half of the body. The hazard of hypotension following subarachnoid injection may be reduced by: (1) limitation of the block to the extremity involved; and (2) prophylactic administration of a full dose of vasopressor drug. Ephedrine, 50 mg., is not dangerous to a patient with hypertension when it is given just before spinal analgesia. A moderate elevation of blood pressure in such a patient is less dangerous than a profound fall. Patients showing mental disorientation preoperatively should receive regional or spinal analgesia by preference. Premedication for the older age group should not include scopolamine. In the case just described, this anticholinergic drug no doubt contributed to the confusion noted during operation—a condition that made the undesirable production of unconsciousness necessary. It is debatable whether anticholinergic drugs are required at all prior to regional methods of pain relief.

Case 5. A 71-year-old colored female weighing 97 pounds was admitted for repair of a femoral hernia. The patient was emphysematous and had dyspnea on exertion. Her blood pressure was 240/115, and her heart was enlarged, but compensation adequate. The electrocardiogram indicated the possibility of an old posterior myocardial infarct. Analgesia was obtained by means of a regional inguinal block, encompassing principally the ilioinguinal, iliohypogastric, and genitofemoral nerves (FIGURE 5). Xylo-

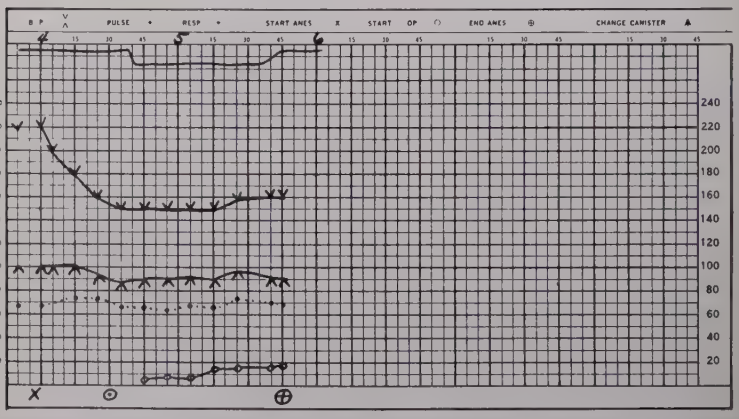

FIGURE 5. Regional inguinal block proved satisfactory for the repair of a femoral hernia in a 71-year-old female. Local analgesic, Xylocaine, 1.0 per cent, 400 mg.

caine, 400 mg. in 1 per cent solution, was used. Supplementary sedation during the procedure consisted of pentobarbital, 180 mg. The postoperative course was satisfactory.

It was believed that the pulmonary and cardiovascular systems of this patient would be least upset by a regional block. Sedation with short-acting barbiturates is less likely to produce mental confusion than with the ultra-short-acting barbiturates.

Case 6. A 74-year-old colored male weighing 170 pounds was admitted for hemorrhoidectomy. The chest X ray showed marked elevation of the left diaphragm, with paradoxical movement indicating paralysis or weakness. This patient had compensated hypertensive cardiovascular disease with cardiomegaly, and the electrocardiogram showed left ventricular ischemia. B. P. 182/118. Caudal analgesia was elected, employing a total of 500 mg. Xylocaine in 2 per cent solution (FIGURE 6). The patient was discharged the day following operation.

Again it was felt that regional analgesia would interfere least with the metabolic functions of this patient.

Case 7. A 75-year-old colored female was brought to the operating room for combined abdominoperineal resection for carcinoma of the rectum. Moderate emphysema was present. There was evidence of moderately severe cerebral arteriosclerosis. Incipient cardiac failure had been treated with slow digitalization. The blood pressure was 180/110. Anesthesia was induced with surital sodium, 200 mg.; intubation was facilitated with succinylcholine, 40 mg.; and anesthesia was maintained for 5½ hours with ethylene, oxygen, and traces of ether, employing a partial rebreathing system with alternating assisted and controlled respirations (FIGURE 7). The patient received 4000 cc. blood. Her general condition remained satisfac-

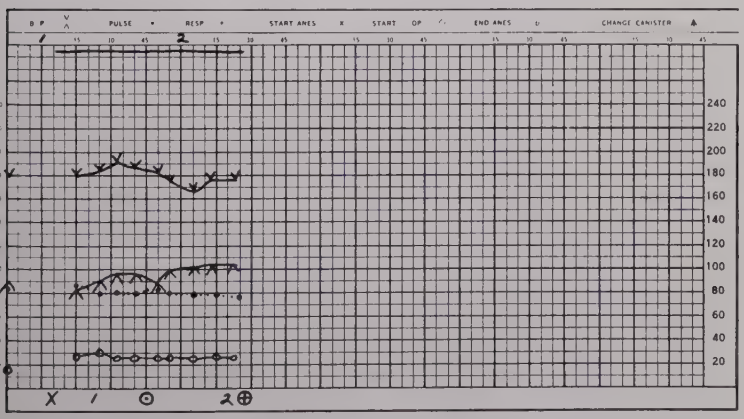

FIGURE 6. Minor surgical procedures such as hemorrhoidectomy can be performed safely under regional analgesia.

FIGURE 7. Anesthetic record of a poor-risk patient, 75 years old, who tolerated a major abdominal procedure satisfactorily under light general anesthesia.

tory throughout the operation and she was mentally clear in the postoperative period.

When general anesthesia is elected, light planes of anesthesia, associated with adequate ventilation of the lungs and replacement of blood to maintain normal circulating volume, help to maintain the status quo of the patient.

Case 8. A 75-year-old white male weighing 130 pounds came to the operating room for removal of a parotid tumor and for associated radical neck dissection. Moderate pulmonary emphysema was present. The blood pressure was 170/95; an X-ray examination showed enlargement of the heart; and the electrocardiogram showed first-degree auriculoventricular block, left ventricular hypertrophy, and left ventricular ischemia. Topical analgesia of the nose and throat was produced with cocaine, 10 per cent, and a transtracheal topical analgesia was obtained with Cyclaine, 2.0 cc. 5 per cent solution. Blind nasotracheal intubation was performed with the patient awake. Anesthesia was maintained for 7 hours by nonexplosive technique with surital sodium, 400 mg., intermittent meperidine drip, 150 mg., and nitrous oxide-oxygen, 70:30, utilizing controlled respirations (FIGURE 8). Transfusions totaling 4000 cc. blood were given. The preoperative and postoperative values for hemoglobin were 12.5 G. The anesthetic course was satisfactory, except at one point when severe bleeding occurred in the region of the carotid sinus. Associated with this bleeding were hypotension and bradycardia, caused in part by probable excessive vagal stimulation. The rapid administration of blood, an intravenous injection of an anticholinergic drug, Antrenyl, and inhalation of 100 per cent oxygen corrected this condition rapidly. TABLE 1 shows that the values for *p*H, carbon dioxide tension, and oxygen saturation of the arterial blood remained normal during the course of anesthesia. The postoperative course in this patient was satisfactory.

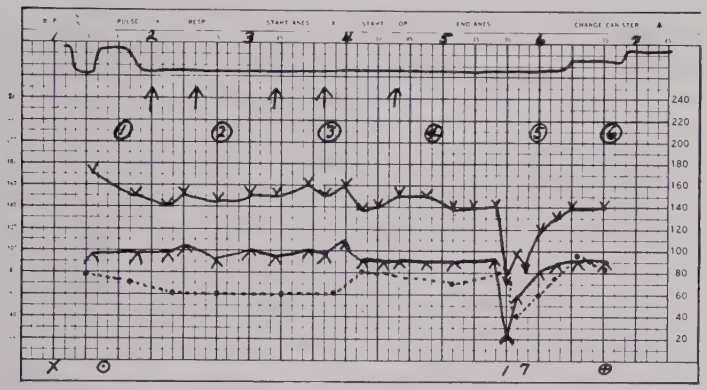

FIGURE 8. Anesthetic record of a 75-year-old male undergoing radical neck dissection. Nonexplosive anesthetic agents and "controlled" respirations were employed.

Thorough topical analgesia prevents undesirable reactions caused by the endotracheal tube, for example, bucking, holding the breath, and coughing, and it reduces the total amounts of anesthetic drugs required during operation. Controlled respirations aid in preserving normal acid-base balance and probably contribute, in some way as yet unknown, to the state of narcosis. When performed properly, they do not interfere with cardiovascular function. When hypotension occurs, the etiological factors must be determined and specific therapy instituted rapidly.

Summary

In geriatric patients the risk of anesthesia and surgery is increased because of the loss of elasticity in the tissues that is associated with the natural process of aging. The areas of primary concern are the respiratory, cardiovascular, cerebral, and renal systems. Acquired diseases, such as carcinoma and diabetes, that may affect the daily metabolic functions, also increase the hazard of surgery. Choice of anesthesia is determined finally by an individual assessment of each patient. Safe anesthesia and adequate

TABLE 1

VALUES FOR *p*H, CARBON DIOXIDE TENSION, AND ARTERIAL OXYGEN SATURATION OBSERVED DURING OPERATION IN THE PATIENT WHOSE ANESTHESIA RECORD IS GIVEN IN FIGURE 8.

	*p*H	P_{CO_2}	O_2 Sat. %	Respiration
1:45	7.42	40.8	78.0	Spontaneous
2:45	7.42	38.8	100.0	Controlled
3:50	7.42	45.7	96.0	Controlled
4:55	7.50	38.0	96.0	Controlled
6:00	7.50	36.2	100.0	Controlled B.P., 70/50 O_2 only
6:45	7.42	45.2	99.0	Assisted closing

operating conditions may be provided by regional or spinal analgesia carefully administered, or by light planes of general anesthesia, associated with the judicious employment of muscle-relaxant drugs, and accompanied by the maintenance of effective alveolar ventilation.

References

1. Knight, R. T. 1954. Geriatric Medicine. **1**: 158. 3rd ed. E. J. Stieglitz, Ed. J. B. Lippincott Co. Philadelphia, Pa.
2. Anglem, T. J. & M. L. Bradford. 1953. Major surgery in the aged. New Engl. J. Med. **249**: 1005–1009.
3. Bedford, P. D. 1955. Adverse cerebral effects of anaesthesia on old people. Lancet. **2**: 259–263.
4. Papper, E. M. 1953. Renal function during general anesthesia and operation. J. Am. Med. Assoc. **152**: 1686–1689.
5. Stephen, C. R. 1955. Anaesthetic and operative problems in the geriatric patient. Can. Med. Assoc. J. **73**: 789–796.
6. Cole, W. H. 1954. Problems in operability. Ulster Med. J. **23**: 102–116.
7. Nicholson, M. J. & F. G. Jensen. 1952. Importance of blood volume studies in management of surgical patients. Current Researches Anesthesia & Analgesia. **31**: 27–35.
8. Howland, W. S., O. Schweizer, C. P. Boyan & A. C. Dolto. 1956. Treatment of adrenal cortical insufficiency during surgical procedures. J. Am. Med. Assoc. **160**: 1271–1273.

Part II. Controlled Respiration in Anesthesia

FACTORS OF SIGNIFICANCE IN THE RESPIRATORY SYSTEM

By William A. Spencer

Departments of Physiology and of Pediatrics, Baylor University College of Medicine; and Southwestern Poliomyelitis Respiratory and Rehabilitation Center, Jefferson Davis Hospital, Houston, Texas

A description of the normal process of respiration and its comparison to artificial pressure breathing appears to be useful in identifying both the remarkable similarities and some important differences between these processes under abnormal circumstances. In the classic mechanical and biochemical sense, normal respiration may be defined as the optimum adjustment of rate, depth, and pattern of breathing that meets the metabolic demand for oxygen uptake and carbon dioxide elimination with minimal expenditure of energy by the respiratory muscles. This definition refers to the quiet, steady state and is therefore of less precise meaning in the unsteady states accompanying extremes of physical activity or during the adjustments occasioned by disease, injury, or the administration of pharmacological agents. In the preparation for, and in the conduct of, general anesthesia the central nervous system, neuromuscular activity, and general cellular metabolism may be affected by the pharmacological agents administered. However, since controlled respiration during anesthesia must meet the needs of metabolism for oxygen uptake and carbon dioxide elimination, this definition has had a primitive durability for the anesthesiologist and physiologist alike.

From a functional viewpoint, respiration can be considered as a critically regulated, autorhythmic vital function, operating ceaselessly in the absence of voluntary cortical or subcortical reflex challenge. Respiratory activation, in its normal ebb and flow, achieves, through its neuromuscular and pulmonary counterparts, a degree of alveolar ventilation that preserves primarily the ratios of oxygen to carbon dioxide and hydrogen to bicarbonate ion in a homeostatic manner. Respiration possesses a capacity for rapid fluctuations in rate, in amplitude, and in pattern of activity particularly suited to the transitory supremacy of purely nervous functions. In this manner the demands of such voluntary activities as verbal communication and emotion, the protective reflexes of coughing and sneezing, and the adjustments to extremes of physical activity are readily met. The chemical regulation so characteristic of the quiet state, and the rapid oscillations in response to changes in the biochemical substratum of the extracellular and intracellular fluids describe but a part of the total function. Biochemical regulation can be considered to sustain the cellular integrity essential for the extensive variations of the respiratory act. Thus the controls that perpetuate the system at one level can be considered preparatory to the range

of activity that may be demanded by co-ordinate cerebral, autonomic, and somatic function. In this way a structure has been evolved for the participation of the act of breathing in the manifold functions making up bodily activity during the adjustments encountered in health and disease.

The Neurogenesis and Regulation of Respiration

Because the genesis, regulation, and mechanical parts of the respiratory act are intermingled, it is useful to describe their interaction. One current and most helpful visualization of the mechanism in the central nervous system that originates respiration and through which it is controlled has been provided by Hoff and Breckenridge. The data on which this concept is based were obtained by experimental ablation of the brainstem in dogs and by pharmacological "dissection" of the patterning of respiration with morphine and *dl*-Dromoran.[1-4] This experimental work in animals has been found to parallel findings in humans suffering from brainstem poliomyelitis[5] or encephalitis, and in cases of morphine[6] or barbiturate intoxication. The animal studies of these authors substantiate the existence of an autorhythmic medullary pacemaker responsible for respiratory activation. Superimposed upon this primitive automaticity, supramedullary neuroregulation appears to activate one or another variant of the respiratory act most suitable for co-ordinate somatic or cerebral activity. FIGURE 1 illustrates an "exploded" view of the dog brainstem with superimposed pneumograph records of the patterns of breathing that are representative of the various levels of respiratory integration. In this schema, "at the medullary level (the decerebrate animal possessing only an intact medulla) breathing is ataxic and irregular in amplitude and frequency."[4] This medullary breathing is capable of sustaining the animal in an acute experiment for as long as 8 to 9 hours.[7] "It is uninfluenced by vagotomy. With addition of apneustic center in upper medulla and lower pons, rate and amplitude of eupnea are regularized, all-or-nothing rhythm is accentuated, and apneusis appears after vagotomy (box on right). Inclusion of 'pneumotaxic' center in upper pons prevents apneusis after vagotomy, but accelerates all-or-nothing rhythm (box on left). With intact cortex, all-or-nothing rhythm is suppressed."[4] Thus, it becomes evident that respiratory activation is subject to supramedullary regulation, which can vary the respiratory act from the extreme of suppression (apneusis) to the release of rapid, gasping, all-or-nothing types of breathing effort in which the normal eupneic pattern is suppressed. Normal breathing patterns characterize the fully integrated mechanism, in which the all-or-nothing rhythm is suppressed. Furthermore, it appears that respiratory regulation is included in the general reticular facilitatory and inhibitory network of the brainstem that modulates autonomic, somatic, and cerebral activity. Recently, cardioregulatory variations have been demonstrated to accompany different levels of respiratory integration in experimental animals.[8] Counterparts in human beings with cardioregulatory dysfunction, such as brady-

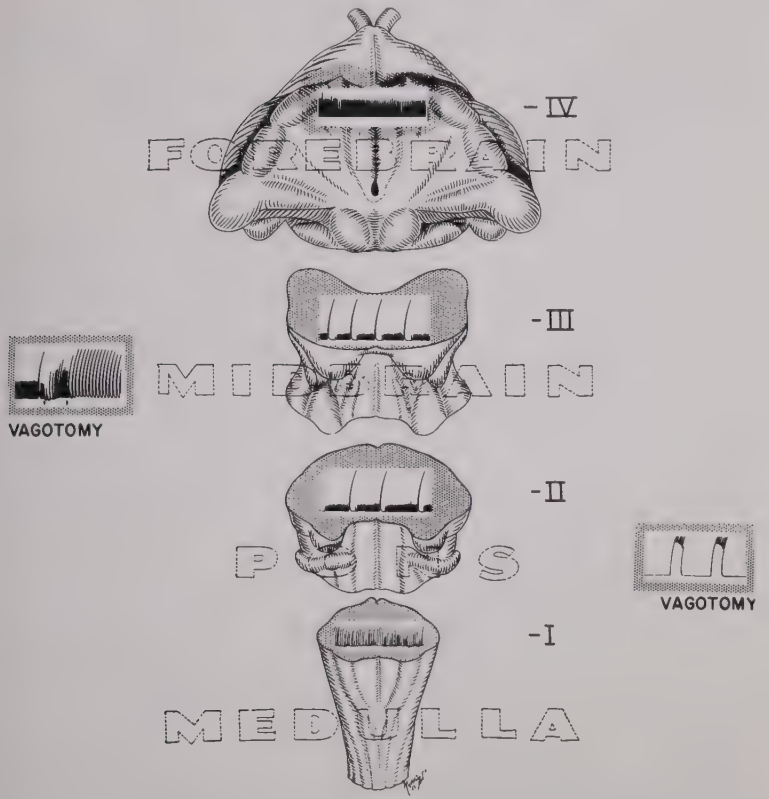

FIGURE 1. Schema of the levels of respiratory integration in the brainstem of the dog. Superimposed pneumograph records indicate appropriate patterns of respiratory activation at different levels of decerebration. Boxes to the right and left indicate the pattern of breathing after vagotomy at the corresponding level. Arrows under the record in the left-hand box indicate the moment of section of the right and left vagus nerve. (H. E. Hoff and C. G. Breckenridge, Figure 478, Chap. 42, p. 853 in *The Textbook of Physiology*, edited by John F. Fulton. 1955. W. B. Saunders Co., Philadelphia, Pa. Reproduced with the permission of the authors and the publisher.)

cardia, embryocardia, rhythm disturbances, and intermittent bundle-branch block have been observed during the course of brainstem viral invasion in poliomyelitis.[5]

There are several general implications of interest to the anesthesiologist in this concept of respiratory genesis and regulation:

(1) The neural architecture described forms a common meeting place in which neural reflexes and biochemical regulators such as carbon dioxide, hydrogen ion, and oxygen can act. Similarly, pharmacological agents such as morphine, *N*-allylnormorphine, and the barbiturates, that affect short,

multisynaptic reticular neurons, are capable of altering the pattern of integration. Therefore, such regulating agents by their site or pattern of action alter the complex interplay of the genesis, regulation, and integration of respiration, and different pathways can lead to the same effect.

(2) The co-ordination of breathing with other vital functions must be taken into account, since disturbances of one may affect another. Furthermore, the appropriateness of alterations of a particular function must be evaluated from the point of view of other related functions.

(3) The manner in which alterations of the nervous mechanism, biochemical disturbances, and mechanical changes in the lungs and thorax contribute to, or modify, the final form of the breathing act must be appreciated. Thus, complete description of the biochemical, mechanical, and neuroregulatory aspects of breathing may be necessary in order to compare various pharmacological agents, or to evaluate the suitability of artificial methods of respiration in the unsteady states.

The anesthesiologist is becoming increasingly aware of the widespread effect of the pharmacological agents that he employs and of the influence of the anesthetic procedure on the pattern of the natural respiratory effort and on cardiac and vasomotor behavior. If vital functions and their interplay are not estimated more completely than at present, difficulties will arise in determining what is normal or appropriate to, or even tolerable by, the patient.

That such considerations of brainstem function are practical may not be immediately apparent. This view is most probably a consequence of rather narrow attention to the biochemical sufficiency of elective artificial respiratory methods. Without doubt, biochemical sufficiency is the essential requirement of such procedures; however, once the surgery is completed and the conduct of anesthesia terminated, the anesthesiologist must determine when the spontaneous mechanism of breathing is adequate and artificial respiration no longer necessary; and he, as well as the clinician, must detect respiratory insufficiency in order to institute appropriate artificial respiration.

Chemical Regulation of Breathing

The response of respiratory minute volume to some of the biochemical participants in its regulation is indicated in order of magnitude in FIGURE 2.[9] It can be seen that increasing the hydrogen-ion concentration in the arterial blood and raising the carbon dioxide tension (during carbon dioxide breathing) increases the minute volume. Both of these regulators influence the minute volume to a greater degree than a progressive decrease in inspired oxygen concentration, although both are capable of "stimulating" the respiratory effort. In this sensitivity of the respiratory mechanism chiefly to carbon dioxide and hydrogen-ion can be seen the basis for carbon dioxide homeostasis in arterial blood. This finding has been elaborated into well-defined schemes of chemical regulation that describe the behavior of the respiratory system in regard to energy metabolism, and oxygen and carbon

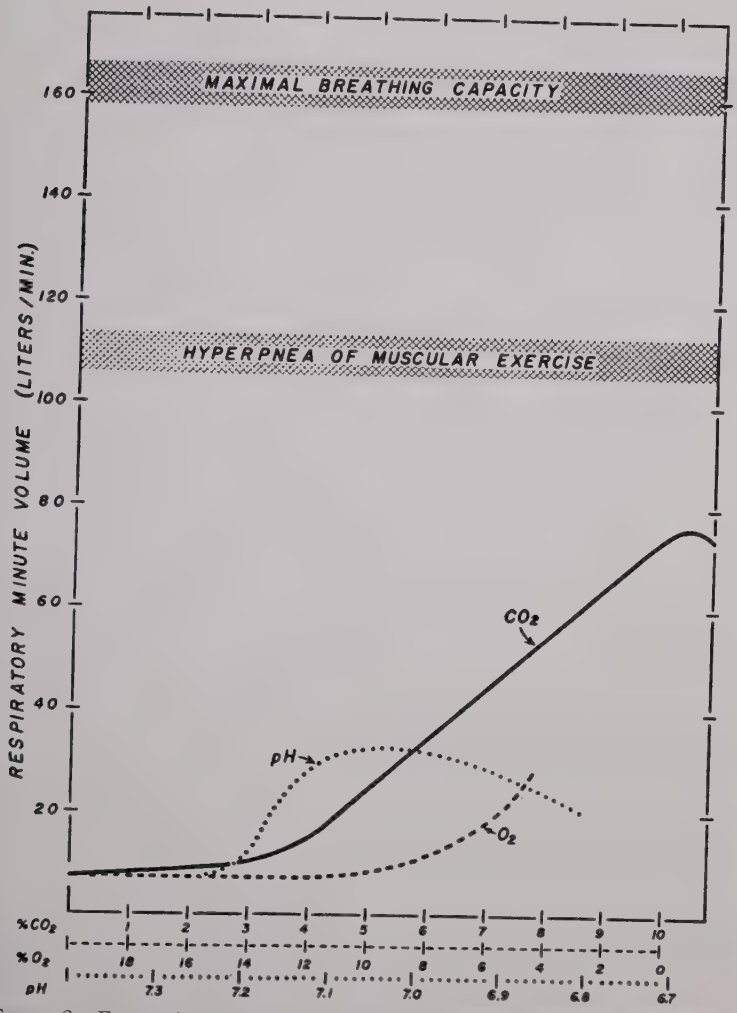

FIGURE 2. Factors in the chemical control of breathing, illustrating the separate effects of alteration of *p*H in the arterial blood in patients with acidosis and during hyperpneas produced in normal man by breathing high carbon dioxide and low oxygen mixtures. The levels of ventilation induced by extreme muscular exercise and during the maximal breathing capacity test are indicated in the crosshatched areas. (J. H. Comroe, Jr. *et al.* 1955. *The Lung*, p. 42. Year Book Publishers, Inc. Chicago, Ill. Reproduced with the permission of the author and the publisher.)

dioxide adjustment. FIGURE 2 also indicates that the magnitude of the hyperpnea of exercise exceeds that of carbon dioxide stimulation and that the effort of the maximum breathing capacity is the most powerful stimulus of all, although not sustained for long. An outstanding characteristic of the hyperpnea of muscular exercise is "its precise adjustment to the metabolic requirements of the organism. In moderate exercise ventilation is directly proportional to oxygen consumption so that a constant ventilatory equivalent (*i.e.*, ventilation/100 cc. of oxygen consumed) is maintained. In severe exercise with oxygen consumptions above 2.0 to 2.5 liters per minute, ventilation increases more rapidly than metabolism and the ventilatory equivalent rises."[10] In such circumstances, at low levels of exercise, elevations of P_{CO_2} can account for the increased ventilation, but at high levels, the changes in P_{CO_2} diminish in magnitude and their contribution to the stimulation of ventilation wanes. Other factors must account for the rising ventilation, but no adequate explanation has yet been offered. It would appear that multiple factors must combine to regulate the final form of the discharge of the medullary respiratory centers.

Studies in oxygen-deficiency states and during metabolic disturbances in man, together with investigation of the effects of biochemical oscillations induced in experimental animals, indicate a hierarchy of chemical regulation. The rapidity of ventilatory adjustments appears to proceed all the way from alterations in hydrogen-ion and bicarbonate-ion or carbon dioxide concentration to oxygen deficiency. Detailed reviews and investigations of this important subject may be found in the works of Gray,[11] Hesser,[12] Bjurstedt,[13] and, most recently, Winterstein.[14]

The response of ventilation to chemical regulation is clearly the result of the summation of all the biochemical factors involved. The control by chemical regulation, while precise, is not so powerful nor so independent that transient cortical and subcortical reflex activity may become dominant.

Mechanical Events Leading to Pulmonary Ventilation

Once an appropriate activation of the inspiratory musculature has occurred, the resulting contraction leads to enlargement of the thoracic compartment, either by means of the descent of the diaphragm or by the contraction of the intercostals, or both. An increase in the volume of the thorax most likely involves initially the most distensible structures within it. The air-bearing alveoli are the most distensible and voluminous portions of the pulmonary parenchyma. Initial enlargement should occur here in direct proportion to the net volume change of the musculoskeletal chamber of the surrounding thorax. As a direct consequence of the increasing volume of the alveoli, a pressure difference develops between them and the oropharynx along the conducting passageways leading to them (transairway pressure gradient). The pressure gradient in which pressure in the alveoli is less than the pressure in the conducting channels leading to them is the

basic physical event responsible for air inflow. Pressure declines in the alveoli because their volume increases. This condition of decreased pressure relative to the airway persists until air inflow into the alveoli introduces a sufficient number of molecules to equal the total density present in a comparable volume of air at atmospheric pressure. In a progressive manner, then, air inflow achieves equalization of the pressure from the oropharynx to the alveoli. This process constitutes inspiration. At the moment of cessation of air inflow there has been introduced a volume of air that is equivalent to the net volume change of the thoracic compartment. Excessive flexibility of the rib cage, resistance to descent of the diaphragm, or paradoxical movement of the chest or diaphragm in the event of muscular weakness or paralysis, simply results in less net volume change for a given amount of muscular work. The position of the body and the amount of intra-abdominal pressure influence the volume distribution and the direction of expansion of the thoracic compartment.

Another physical law operates at the alveolar level. This is the tendency of a mixture of gases to assume equal and uniform distribution in partial concentration by the process of diffusion, while the total pressure remains the same. In the absence of airflow from the alveolar duct to the alveolus, it is possible for molecules to diffuse between these 2 chambers until equal concentrations of like gases are achieved. In this way, the partial pressure of oxygen in the alveolus may be elevated and that of carbon dioxide lowered, because the gas concentrations in the diluting incoming air are higher in oxygen and lower in carbon dioxide than the average alveolar gas mixtures. The extent to which this process operates to replenish the atmosphere of the alveoli is not known.

As a result of inflation of the lungs, increasing neurogenic inhibition of inspiratory muscular activation develops until finally contraction ceases. Upon relaxation of this active muscular effort, the energy stored in the pulmonary tissues as a result of their elastic deformation or stretch becomes available to compress the volume of the lungs and to reduce the dimensions of the thorax; thus a reversal of pressure difference in relation to the airway is achieved and air outflow results. This process constitutes expiration. It is noteworthy that, as a result of favorable changes in airway caliber during expiration, the frictional resistance to air outflow is less than that encountered on air inflow. Furthermore, a unit-volume decrease of the inflated lungs is accompanied by a smaller unit-pressure change. This finding is probably a result of the altered mechanical properties of the inflated lungs.

In the quiet state, expiration is passive. However, active contraction of the expiratory musculature and elevation of intra-abdominal pressure cause a rapid diminution in thoracic volume, and produce active expiration.

Figure 3 shows that the events of muscular contraction leading to enlargement of the lungs, the development of a pressure gradient, and the inflow of air are in reality nearly simultaneous occurrences. In the record shown here, muscular contraction is indicated by enlargement of the cir-

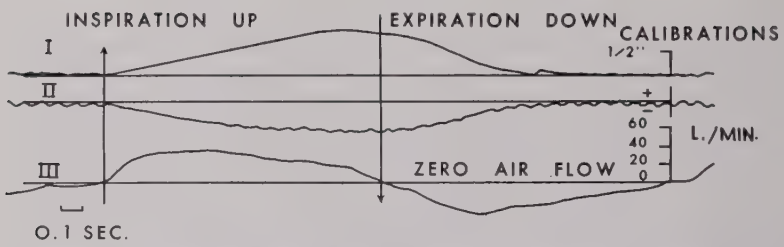

FIGURE 3. Physiograph record of chest movement, fluctuations of esophageal pressure, and air inflow and outflow. This record is taken from an adult male subject who had a paralysis of the left diaphragm due to a stab wound of the neck that severed the left phrenic nerve. Channel I is the record of thoracic expansion recorded with a photoelectric pneumograph (expansion upward); Channel II, intraesophageal pressure fluctuations, recorded by means of a photoelectric pressure transducer connected to a polyethylene balloon-tipped esophageal catheter, referred to oral pressure (decreases downward); and Channel III is a pneumotachograph record of airflow velocities recorded through a Silverman-Whittenberger mask connected to a capacitance condensor-type pressure transducer (inflow upward). The coincidence of the onset of thoracic movement, decline in esophageal pressure, and onset of air inflow is graphically recorded. The first half of the record indicates inspiration, and the second half, expiration. Onset of inspiration and onset of expiration are indicated by the vertical lines.

cumference of the thorax. Esophageal pressure is considered representative of some portion of alveolar pressure change, as is true of intrapleural "pressure" fluctuations. Velocities of air inflow and outflow at the oral airway are self-evident. From this record it is clear that these events coincide closely in time of onset. The time interval between these events cannot be greater than 16 msec., which is the upper limit of response of the recording apparatus.

The special efficiency accruing to the breathing musculature by virtue of the mechanical arrangement of the lungs and thorax is worthy of mention. Because a state of balance exists at the resting expiratory level, little momentum need be imparted to the lung-thorax system to promote thoracic expansion in ordinary quiet breathing. This unique mechanical balance at the resting expiratory level is a consequence of the tendency of the partially inflated lungs to shrink in volume and of the thorax to increase in volume by virtue of its ligamentous and musculoskeletal configuration. This null position is attained because these opposing forces can seek an equilibrium position at the moist pleural interface that permits sliding movement adjustments in the pleural surface area and yet resists mechanical separation.

These opposing forces—elastic recoil of the lungs and the tendency of the thorax to assume a larger volume—are relatively small when compared with the forces operating to keep the pleural surfaces in contact. In fact, separation of the pleura is unlikely because of the much greater clamping effect of coherent moist surfaces and because the pressure of the atmosphere acting across the thoracic-pleural boundary is nearly equal to that acting through the airway across the pulmonary-pleural surface. That there are

opposite forces acting to separate the pleura is readily demonstrated by intrapleural "pressure" measurements; the opposing forces express themselves as a subatmospheric pressure difference when the pleural surfaces are actually separated and cohesive hydrostatic forces and atmospheric pressure become inoperative. Their presence is also detectable in the resting subatmospheric pressure of air-containing hollow structures—for example, the esophagus—contained within the thorax. In view of this, esophageal pressure, obtained by proper placement of a balloon-tipped catheter or an open-ended catheter, is considered to represent adequately this component of intrapleural forces and, to some extent, to represent fluctuations in intrapulmonary pressure.

The fluctuations of esophageal pressure should be considered as summations of increasing or decreasing intrapulmonary pressure plus the contribution of the variable and static pulmonary elastic and thoracic force components acting at the pleural interface. During breathing, these force resultants are of twofold origin: first, the actual intrapulmonary pressure generated from the volume changes of the lungs as a consequence of contraction of the respiratory muscles, in which there is a lag in equilibration of lung volume due to air-inflow resistance and, possibly, as a result of variations in alveolar recruitment during inflation; and, second, the intrapleural "pressure" force, which varies directly with the degree of elastic deformation of the lungs and the position of the thorax. Thus, intraesophageal pressure is not the same as intra-alveolar pressure, although its changes are related to it.

By referring the esophageal pressure to airway pressure at the point of inflow and by computating the pressure at moments of zero airflow, it is possible to separate the pressure components related to elastic deformation of the lungs at different lung volumes. Continual registration of esophageal pressure also permits subtraction of the partial pressures representative of elastic deformation at various increments of lung volume change. Thus it is possible to indicate the portion of the recorded pressure involved in overcoming frictional resistance to air inflow during inflation. The precise and quantitative relationship of such pressures to the actual work of breathing is less clear. However, such pressure studies have been valuable in the analysis of the mechanical behavior of the lungs and thorax. Such data have been particularly useful in identifying air inflow and outflow resistance changes and alterations of pulmonary elasticity. Mechanical analysis of this sort is not new; it was first amplified in 1915 by Rohrer,[15, 16] then by Neergaard and Wirz,[17] and more recently by Otis[18] and Mead.[19]

The Relationship of Artificial Respiration to Natural Respiration

Since it has been established that attainment of a transairway pressure gradient is the prime event responsible for air inflow and outflow, it should not be surprising that the application of suitable pressure across the airway or around the thorax results in air movement into and out of the lungs.

Thus this establishment of a positive airway pressure gradient is the same as that which occurs in natural breathing. It is here in the fundamental equivalence of airway and intrapulmonary pressures that artificial respiration and natural breathing can be considered identical in terms of movement of a volume of air into and out of the lungs. In the absence of muscular action the creation of a pressure difference across the lungs by a mechanical device remains the basic cause of the ventilatory act.

A fundamental consideration in the application of artificial respiration is the identity of the volume changes produced by elevating the pressure at the airway or lowering the pressure around the lungs. FIGURE 4, redrawn from Whittenberger,[20] indicates the comparable volume changes produced by "positive" and "negative" pressure breathing applied to isolated dog lungs. Elevation of the pressure above the atmospheric at the airway

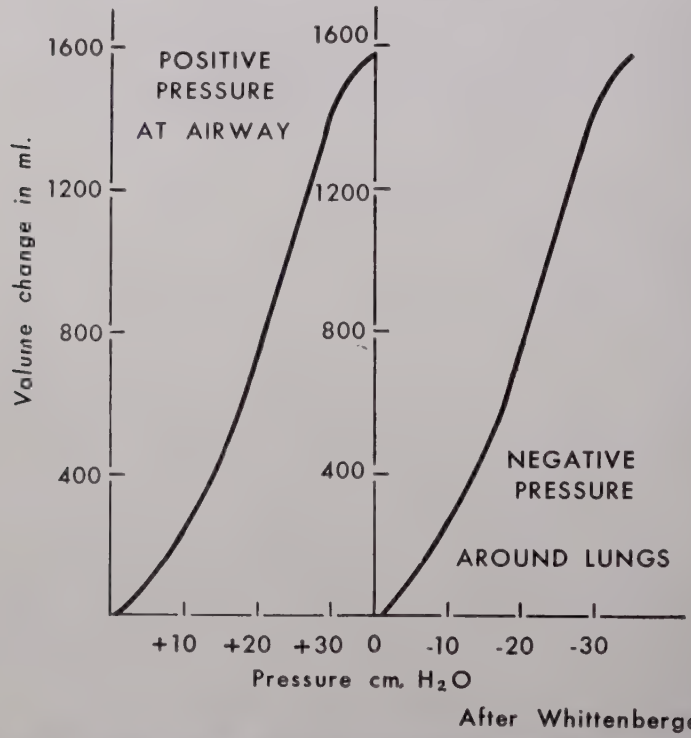

FIGURE 4. Volume changes produced by positive and negative pressure applied to dog lungs. The comparable volume changes produced by 2 methods of inflation of isolated dog lungs are shown. On the left, elevation of pressure in the airway, the so-called "positive" pressure inflation, is indicated; on the right, lowering of pressure around the lungs, the so-called "negative" tank respiration, is shown. (Redrawn after Whittenberger.)

creates a pressure difference favoring air inflow, just as lowering the pressure around the lungs makes the pressure in the airway positive relative to the pressure around the lungs. These identical pressure differences produce equal volume changes. Thus, a difference in pressure of 770 mm. of mercury (plus 10 mm. at the airway) to 760 mm. of mercury in the lungs is the same as 750 mm. of mercury (minus 10 mm.) around the lungs with the airway at 760 mm. of mercury. The only difference between the 2 methods of producing a pressure gradient is that due to the slightly greater gas density at the higher pressures. For practical purposes, at the same frequency of inflation the pressure difference is the same, and the pressure in the airway in either case is positive relative to the lungs.

The energy necessary for artificial pulmonary ventilation is provided in the applied pressure. The peak-pressure difference representing a given degree of lung inflation is the same as that from contraction of the respiratory muscles in natural breathing. Thus, the same pressure gradients achieved by either method should have volumetric equivalence if the position of the thorax and the resting lung volume are the same in each case. That this appears to be true is indicated in FIGURE 5. In this study, 5 relaxed, normal, trained, adult male subjects of comparable body surface area were placed in the tank respirator in the supine position. Respirator pressures were varied from -5 to -25 cm. of water relative to atmospheric pressure. There was a constant cycling of 14 breaths per minute. The effective peak applied-pressure difference was obtained by differential recording of intratank and intraoral pressures during measurement and artificial respiration. In this manner, correction could be made for the inflow and outflow limiting resistance of the measuring devices, and the true peak applied pressure across the lungs and thorax could be obtained at the instant of zero air inflow on a simultaneous pneumotachographic record. There is agreement between our average pressure-volume relationship of 70.5 ml./cm. of peak transairway pressure and that obtained by Rahn *et al.*[21] These investigators, using trained adult male subjects, measured oral pressure at various volumes of voluntary lung inflation at the moment of zero air movement and during presumed complete muscular relaxation. In this manner they obtained a relaxation pressure-volume curve with an average slope of 85 ± 31 ml./mm. Hg relaxation pressure (65 ml./cm. of water). Thus, there appears to be volumetric equivalence of peak transairway pressure gradients in normal individuals during tank respirator respiration and after voluntarily produced lung volume changes in the supine position.

Factors Determining the Ventilatory Efficacy of Applied Pressure

It has been shown that the lung volume changes produced by a given peak applied transairway pressure gradient are comparable in direction and magnitude in healthy subjects of similar size. During the ordinary use of pressure breathing apparatus much greater variation is encountered in the ventilatory efficacy of a given applied pressure. In studies such as the one illustrated in FIGURE 5, complete relaxation and co-operation of the

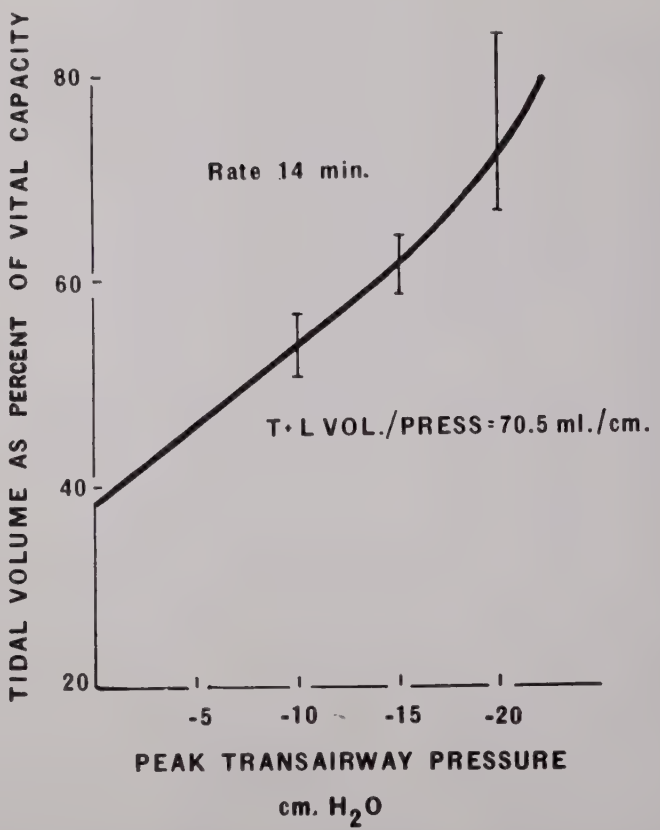

FIGURE 5. Tank respirator pressure-volume diagram. Respirator pressure-volume diagrams, calculated as percentage of measured vital capacity, are shown for 5 normal adult male subjects of comparable body surface area (1.85 to 2.0 sq. m.) and similar age. Tidal volumes produced by peak transairway pressure gradients are expressed as a percentage of measured vital capacity along the vertical dimension. Peak transairway pressure gradients at the instant of zero inflow, obtained by differential intratank and intraoral airway recording, are plotted along the horizontal dimension. Comparable resting expiratory levels were assumed for the purposes of plotting. The average curve for the measurements is indicated by the bold curve, and the total range of variation of the individual curves is indicated by the vertical lines at representative pressures. The average slope indicates a lung-thorax PV value of 70.5 ml./cm. of water pressure.

subjects is an obvious requirement for comparability. However, other factors accounting for the differences often observed in clinical practice should be identified. The variables include: (1) the magnitude of the *effective* mean pressure and its duration in the breathing cycle; (2) the pattern of the applied pressure curve; (3) the mechanical properties of

the lungs, thorax, and abdomen of the subject; (4) the net volume of the pulmonary tissue exposed to the applied pressure gradient; and (5) the resting lung volume and the position of the thorax from which inflation occurs.

Clearly, the volume of air exchanged during artificial respiration with the same apparatus is directly proportional to the magnitude of the *effective* peak pressure applied. This has already been illustrated in FIGURE 5 for the tank respirator. Increasing peak pressure is associated with increasing lung volume changes up to the limits of expansion of the lungs and thorax; there is, of course, a direct relation to body size.

The duration of the mean applied pressure, which defines the average time during which an average pressure is available to promote inflation, is a direct function of the cycling rate of most devices. FIGURE 6 illustrates this relationship schematically in a normal subject in whom adjustment of the cycling rate of the tank respirator, maintaining the same peak applied pressure and average pressure, produced a tidal volume of 450 ml. at a rate of 14 cycles per minute and a tidal volume of 350 ml. at a rate of 22 cycles per minute. The difference in the tidal exchange is primarily the result of the shorter time interval during which the same average pressure

FIGURE 6. Mean pressure duration as a function of cycling rate during artificial respiration. Tidal volumes achieved during tank-respirator respiration in a normal subject at the same peak applied pressure, but at 2 different rates of cycling, are indicated in this schematic illustration. The upper pair of curves indicates time relationships of the pressure curve and of the air inflow and outflow velocities at a rate of 14 cycles per minute; the lower curves show the values for these variables at a rate of 22 cycles per minute. The amplitude of the mean pressure is seen to occur at the midpoint of the sine-wave pressure curve of the tank respirator; its duration up to the instant of zero air inflow is indicated by the crosshatched areas below the upper and lower pressure curves, respectively. The smaller area of mean pressure application in the lower illustration is apparent. Dotted lines indicate the coincidence of peak flow and zero flow in a single cycle. Horizontal and vertical scale units are arbitrary. To the right of the illustration are indicated the actual tidal volume measurements corresponding to the 2 cycling rates.

acts. The mean pressure as a function of time is indicated in the cross-hatched areas under the pressure curve; it can be seen that the area is less at the higher breathing rate than at the slower rate. The assumption is made that there were only slight differences in airflow resistance at the 2 rates of breathing. This may be partly correct, since the peak inflow velocities were nearly the same and did not exceed 40 l./min. Measurements of airflow resistance would be necessary to establish the validity of this assumption since, as the frequency of breathing increases, air inflow resistance increases. This increased resistance introduces another important effect of rate for, at extremes of rapid breathing in normal subjects or at slower rates in the presence of bronchiolar constriction, reduction occurs in the volume of air moved for a given duration of pressure. Presumptive evidence was obtained that, at the rates chosen in this normal example, the latter factor was minimized by the coincidence of peak inflow velocity at comparable pressures. It should then be appreciated that the frequency of cycling of a respiratory device affects both the duration of the mean or average pressure applied and the development of inflow resistance within the subject as well as within the apparatus itself. These effects alter the volume of air introduced into the lungs for a given peak pressure. Obviously, variations in the proportion of inspiration to expiration will influence the total time per minute in artificial respiratory devices, in which a given average pressure is available to promote air exchange.

The second variable of pressure pattern within the same duration of mean pressure has not been extensively investigated in comparable circumstances. It is possible that alterations in the shape of the curve for applied pressure may be made to coincide more closely with the changing reluctance of the lungs and thorax to inflation and to alterations of airflow frictional resistance. In this manner pressure patterns may influence the rapidity and uniformity of alveolar recruitment during the inflation of the lungs. Thus, the spatial distribution of the same volume of air introduced may vary, depending upon the time relationship and the uniformity of alveolar inflation. Differently phased intrapulmonary pressure gradients may vary in their effectiveness for opening collapsed and moist bronchiolar and alveolar duct passages. According to Day,[22] square wave-pressure patterns of brief duration have been held to be more effective in the *initial* inflation of atelectatic animal lungs and, possibly, newborn lungs. There are too little data to outline clearly the role of different pressure patterns in normal subjects, and even less in the presence of pulmonary disturbances such as atelectasis.

Just as the mechanical properties of the lungs and thorax influence the work of natural breathing, they also determine the ventilatory effectiveness of artificial pressure breathing. In fact, the mechanical behavior of the subject is of major importance. As in the case of natural breathing, the pressure work involved in enlarging the diameters of the thoracic compartment must overcome: (1) the reluctance of the partially inflated lungs to be further distended (by virtue of their elasticity); (2) the frictional re-

sistance to air movement in the air passages; and (3) the friction generated from the movement of the thoracic and pulmonary tissues and in the displacement of the abdominal contents. The first 2 factors account for the bulk of the pressure "work," since a considerable portion of it is utilized in stretching the lungs or overcoming their elasticity and in neutralizing the frictional resistance to the air flowing into them.

The manner in which applied tank-respirator pressure is utilized to achieve inflation of the lungs and enlargement of the thoracic compartment is schematically indicated in FIGURE 7. The uppermost hypothetical curve

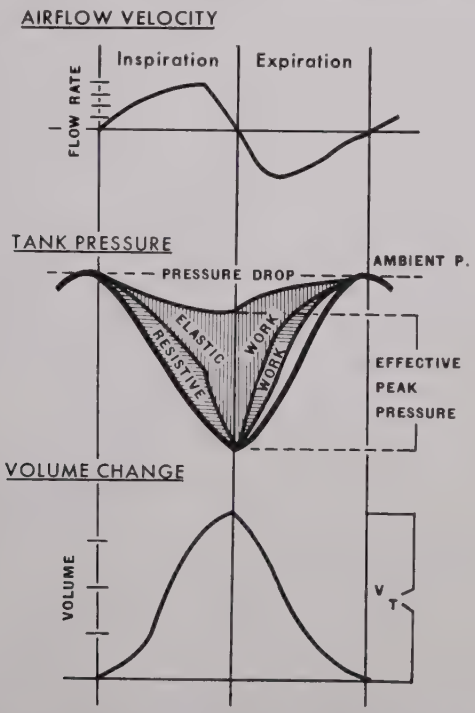

FIG. 7. Schematic relationship of respirator pressure to pulmonary airflow and volume changes. These variables are illustrated in the 3 curves during tank-respirator breathing at a slow cycling rate. These curves have been idealized from measurements in normal subjects. The upper curve illustrates a typical pattern of air inflow and outflow velocity. The middle drawing indicates the subatmospheric pressure excursion of the intratank pressure. Pressure drop refers to the lesser subatmospheric excursion of oral mouthpiece pressure as a result of flow resistance through the measuring and recording devices. Effective peak pressure is indicated as the pressure gradient across the lungs and takes into account the pressure drop. Ambient pressure is indicated by the horizontal dashed line. The pressure curve area is subdivided by crosshatching into hypothetical pressure work areas used to overcome the airflow resistance and the elastic properties of the lungs and thorax combined. The lower record indicates the tidal volume (V_T) excursions of the lungs and the volume integral of the airflow record.

illustrates the changing pattern of air inflow and outflow; the middle record indicates the tank-pressure gradient during the cycling of the device; and the bottom record indicates the volume of air moved at different points during inflation and deflation. The pressure record, which is seen to vary below the base line of atmospheric pressure, demonstrates that the mouth-to-alveolus pressure gradient is always positive relative to the intratank pressure, since the alveolar pressure is presumed to follow closely the direction of the excursions of tank pressure.

The area of the pressure curve has been subdivided into hypothetical areas of: elastic pressure work, necessary to distend the pulmonary tissues and to enlarge the thoracic compartment; and resistive pressure work, used to overcome airflow resistance. The work done to overcome tissue viscous properties and to displace abdominal contents is considered negligible at the slow cycling rate of 12 cycles per minute and in the supine position. It can be seen that the work necessary to overcome elastic deformation is greater than that required to overcome airflow resistance. This is in accordance with observations at slow rates of pulmonary inflation and with relatively large tidal excursions.[23] Air inflow can be seen to start at the beginning of the pressure change. The peak inflow occurs before the peak pressure. The ratio of peak pressure to the total inflow volume at the instant of zero flow between inspiration and expiration describes the static elastic behavior of the system. It does *not* indicate the pathway of inflation. This depends upon the pattern of inflation, which varies with inflow frictional resistance, the spatial distribution of lung expansion, and the force expended in moving the lungs and thorax and in displacing the abdominal contents. In this diagram, the simplification of total pressure work into elastic and airflow frictional work is arbitrary.

The expiration portion of the middle diagram is somewhat misleading: if the applied pressure were to drop to zero at the onset of expiration, the energy available from elastic recoil would be sufficient for expiration. Thus, the expiratory pressure area is really superfluous. The figure does indicate that the pressure area of work is less on deflation than on inflation, a finding that coincides with observations in normal subjects.

These relationships have some value in clarifying the importance of changes in elastic and resistive behavior. Thus, if airflow resistance is increased, a larger pressure work area is expended in overcoming it, and less pressure work is available for elastic deformation. Hence the total volume of air exchanged for a given applied pressure is less in this situation.

The interplay of the mechanical properties of the lungs and thorax in determining the volume equivalent of a given applied pressure is well illustrated in the comparison between the tank-respirator pressure-volume relationships of normal and poliomyelitis subjects shown in FIGURE 8. Tank-respirator pressure-volume characteristics are demonstrated in this figure for 6 normal and 6 matched poliomyelitis subjects with extensive respiratory muscle paralysis. Pre-illness body surface areas of the poliomyelitis subjects and of the normal subjects were comparable, and they

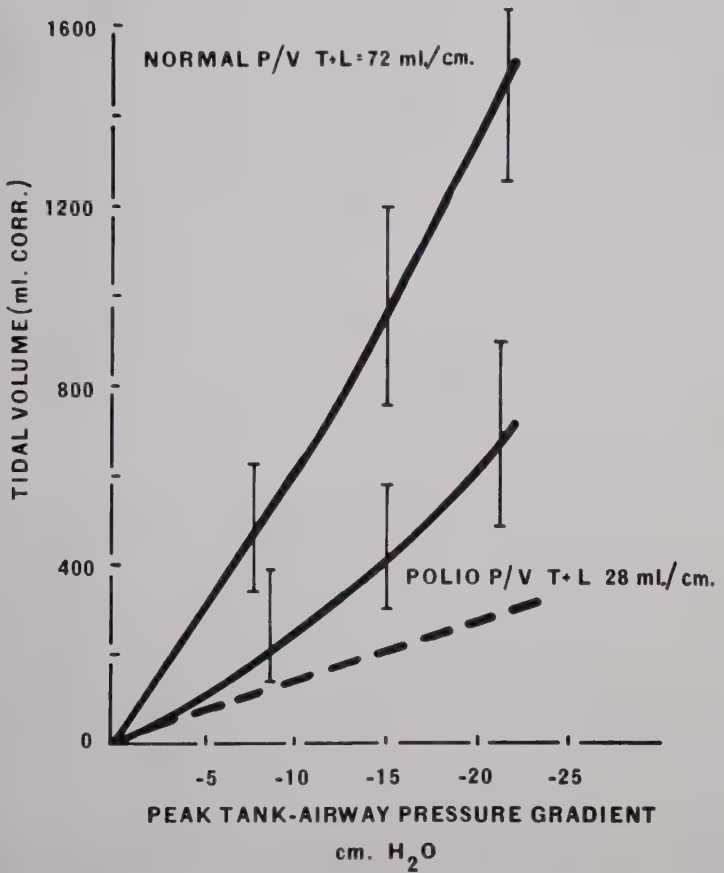

FIGURE 8. Tank-respirator pressure-volume relationships of normal and poliomyelitis subjects. In this figure, healthy adult male subjects were compared to poliomyelitis subjects of similar age range and pre-illness body-surface area (range 1.75 to 2.05 sq. m.). Tidal volumes produced by pressure excursions of the tank-type respirator are plotted in ml. along the vertical dimension. Peak transairway pressure gradients at the moment of zero inflow between inspiration and expiration are indicated in cm. of water along the horizontal dimension. The upper solid curve represents the average of measurements on 6 normal subjects; the lower curve the average of 6 poliomyelitis subjects with varying degrees of respiratory muscle paralysis (vital capacity measurements from 0 to 1200 ml.). The dashed line represents the pressure-volume curve for the largest poliomyelitis subject with a 0 vital capacity. The vertical lines represent the entire range of variation of the individual curves at appropriate pressure increments, with the exception of the single poliomyelitis subject indicated in the lowest dashed line.

varied from 1.75 to 2.05 sq. m. All subjects were in the same age range of 25 to 30 years and were measured supine in the same tank respirator. Because of the inaccuracies of predicted vital capacities in poliomyelitis subjects with suspected changes in total lung capacity as a result of the disease, we undertook a comparison of the tidal volumes alone. The tidal volumes of these subjects were compared at cycling rates that did not vary by more than 2 cycles/min. It can be clearly seen that a given peak transairway pressure gradient achieved roughly one third as great a tidal volume in poliomyelitis subjects as in the normal relaxed subjects. The average slope of the combined pressure-volume curve, which is related to the mechanical properties of the lungs and thorax, was only 28 ml./cm. peak pressure for the poliomyelitis subjects.

Here the remarkable differences are not causally separated, but may be expected to be a result of: (1) alterations in the elastic behavior of the lungs and, to a lesser extent, of the thorax;[24] (2) increased airflow resistance;[25] (3) altered inflation pathways due to changes in the total lung capacity and in the partial inspiratory position of the rib cage; and (4) possible changes in the viscous properties of the pulmonary tissue due to vascular engorgement.

Altered mechanical properties of the lungs and chest during general anesthesia have been reported recently by Nims, *et al.*[26] FIGURE 9, reproduced from the paper of these investigators, illustrates the changes in the relaxation pressure-volume characteristics of normal subjects prior to and after the administration of neuromuscular blocking drugs and anesthetic agents. The Rahn technique was used for the relaxation pressure-volume measurements. It is clear that after induction of anesthesia there is an average decrease in volume changes at a given pressure. This decrease is about 25 to 30 per cent at the higher pressures and larger lung volumes. While these changes are not as marked as those observed in poliomyelitis, the observations of Nims and his colleagues indicate that it is unwise to assume normal mechanical behavior of the lungs and thorax under the conditions of anesthesia, much less in individuals with thoracopulmonary disturbances such as respiratory poliomyelitis. It is quite probable that such methods of study will find a useful place in the evaluation of the effect of different techniques used in anesthesia.

The effect of the net volume of pulmonary tissue exposed to the applied pressure gradients is of little comparative importance in the case of tank-respirator pressure breathing or intermittent-pressure breathing applied to the airway. As has already been indicated in FIGURE 4, there is little difference in so far as the volume equivalents of equal pressure gradients are concerned. The pressure gradients can be expected to have the same relationship to the lungs in either case when it is appreciated that each method produces a positive gradient in the airway relative to the total volume of the lungs. The presence of atelectasis or bronchial obstruction would have an identical effect in either case, reducing the net volume of lung tissue available for expansion.

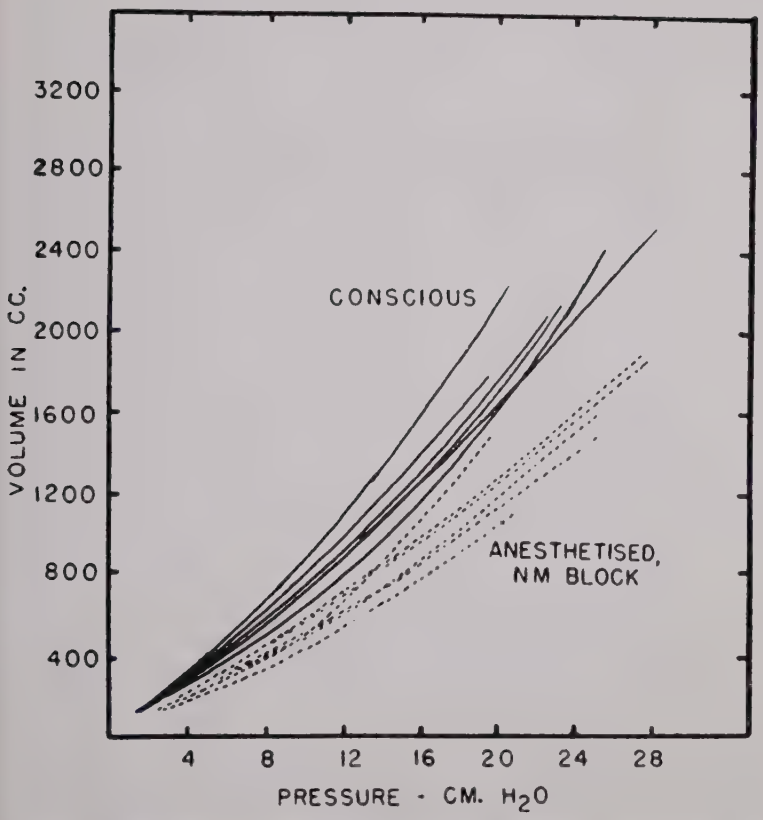

FIGURE 9. Comparison of values for compliance in 6 patients in the conscious, relaxed state and after apnea induced by succinylcholine and anesthesia. Solid lines represent the pressure-volume relaxation curves of 6 subjects before administration of the anesthetic agent and neuromuscular blocking drugs. Dashed lines represent the curves obtained after administration of drugs. (From R. G. Nims *et al.* The Journal of Clinical Investigation. 1955. Vol. 34, p. 744. Reproduced with the permission of the author and publisher.)

On the other hand, the less complete coverage of the thorax and abdomen when such auxiliary breathing aids as the chest or chest-abdomen cuirass respirator are used can be expected to produce smaller tidal exchange for a given intrashell pressure. This is clearly demonstrated in FIGURE 10, in which the tidal volume produced at comparable intrashell pressure excursions has been determined in the same poliomyelitis subject with the different cuirasses and the tank respirator.[27] From this example it appears that the chest-abdomen shell is more effective than the chest cuirass and that both are less effective than the tank respirator. This has been previously reported by Collier.[28] The decreasing effectiveness of such devices, de-

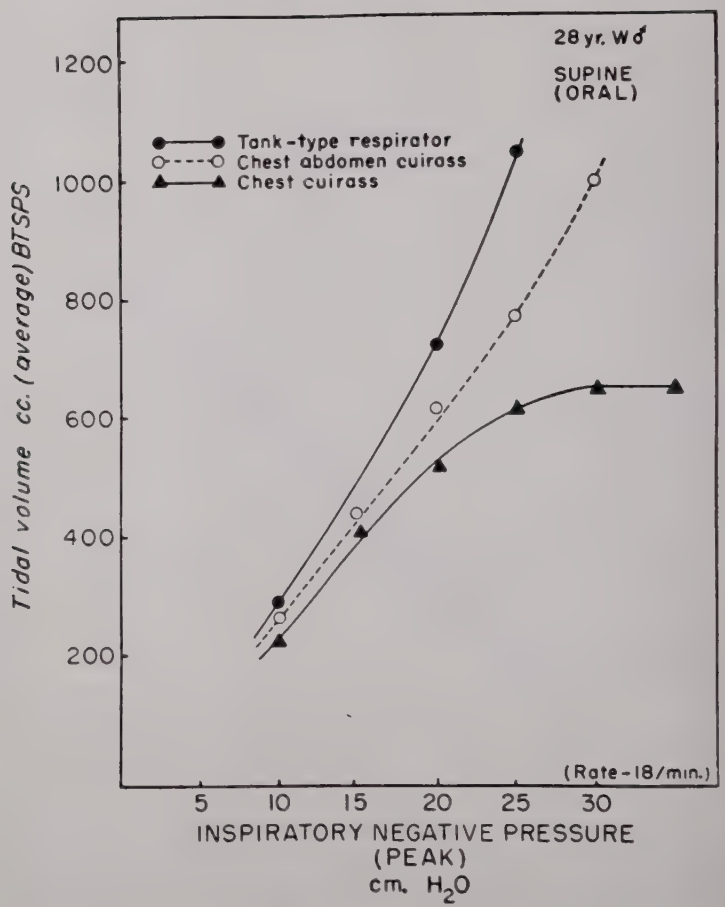

FIGURE 10. Pressure-volume curves for a poliomyelitis subject during tank-respirator and cuirass-respirator ventilation. The curves were obtained by measurement of the tidal volumes produced at the same rate of cycling. The pressure across the oral airway of the subject was determined in the manner described in FIGURES 5 and 8. Peak pressure fluctuations within the tank or the cuirass at the moment of zero airflow between inspiration and expiration are indicated along the horizontal dimension. Tidal volumes in cc. are indicated along the vertical dimension. The decreasing effectiveness of a given pressure gradient is illustrated in the family of curves: the highest curve represents the tank respirator; the middle curve, the chest-abdomen cuirass; and the lowest curve, the chest cuirass. The last curve is flat beyond a pressure of 25 cm. of water and may actually decrease at higher pressures due to restriction of diaphragmatic displacement. The subject had a vital capacity of less than 200 ml. at the time of measurement and had abdominal muscle paralysis. (This figure is modified from an illustration on p. 179 of *Treatment of Acute Poliomyelitis*, by W. A. Spencer *et al.* 1956. Charles C. Thomas. Springfield, Ill. Reproduced with the permission of the publisher.)

pending upon the area of the pulmonary tissue exposed to their pressure fluctuations, may be of greater consequence in the presence of reduced "compliance" or elasticity.

The influence of the resting lung volume and of the position of the thorax and diaphragm is, in part, inseparable from the mechanical properties of the lungs, thorax, and abdomen. Special emphasis is accorded to these factors because: (1) changes in the resting lung volume and in the anatomical position of the thorax most often occur in the direction of partial inspiration and, therefore, further inflation of the lungs may proceed along a different and flatter portion of the normal pressure-volume inflation curve; and (2) the dilution of a given inspired volume may be of physiological significance when the functional residual capacity is increased or decreased due to different positions of the body or as a result of restrictions to thoracic enlargement. The first consideration implies that, if the resting expiratory level of lung volume is increased absolutely, by increased functional residual capacity, or relatively, by virtue of an inspiratory position of the thorax or a low diaphragm position, a given applied pressure will produce a smaller volume change than might be expected ordinarily. This is a direct result of the increasing reluctance of the lungs and thorax to enlarge further at large lung volumes or in mechanical inspiratory positions of the rib cage approaching 60 to 70 per cent of the total lung capacity. Hyperextension of the spine and intercostal muscle paralysis may cause relative changes in the resting expiratory level, in contrast to the absolute increase in residual lung volume observed with anatomical emphysema due to bronchiolar constriction. Similarly, abdominal distention, leading to a high diaphragm position and an increased resistance to downward movement, may require a greater degree of thoracic inspiratory movement or displacement than normally occurs in the supine position during artificial respiration.

The manner in which the functional residual capacity varies with different body positions is indicated in FIGURE 11. These measurements of pulmonary compartition in a healthy adult male subject coincide with the observed increase in functional residual capacity in the standing position. The increase appears to be due to the higher starting position of the diaphragm in the supine position (as determined by fluoroscopic measurements) leading to a larger inspiratory capacity. An increased ability to achieve active expiration through forward flexion of the spine in the standing position and through more effective abdominal muscular contraction can account for the increased expiratory reserve volume in this position. The resting expiratory level is obviously at a larger volume of the total lung capacity in the standing position. There is some variation in the proportionate changes in individual healthy subjects of comparable body size, depending in part upon the configuration and dimensions of the thorax.

Although this study is not directly applicable to the situations encountered in anesthesia, careful estimation of the shifts in resting expiratory level and pulmonary compartition should be made in the semiupright, head-down, side-lying with lateral flexion, supine, and prone postures employed

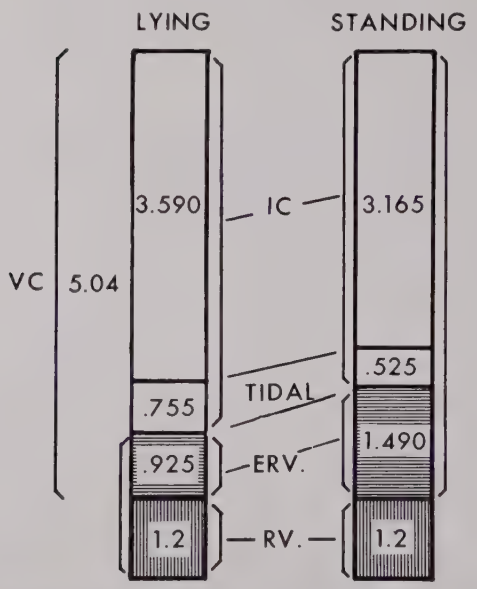

FIGURE 11. Compartition of total lung capacity of a healthy, adult male subject in the lying and in the standing positions. Measurements were made with a closed-circuit spirometer and are expressed in liters (corrected to standard pressure and body temperature). Total lung capacity equals 6.24 l. In the standing position, inspiratory capacity (IC) decreased and expiratory reserve volume (ERV) increased. Vital capacity (VC) was unchanged. Residual volume (RV) was assumed to be the same and to equal predicted values for this age and body size. Functional residual capacity, while not indicated, is equal to the sum of ERV and RV.

for various surgical procedures. Such a determination will be essential if at the same time the ventilatory effectiveness of applied pressure is being estimated, not only in terms of the pressure-volume relationships, but also in terms of the physiological equivalence of a given tidal volume. In the latter instance, the changing ratios of tidal volume to increasing or decreasing functional residual capacity may be expected to have physiological significance.

Factors Influencing the Physiological Equivalence of Artificial Respiration

As soon as it is appreciated that residual anatomical compartition refers to a static situation and that the volumes in the different compartments are constantly intermixed to a variable degree in the course of pulmonary inflation and deflation, the crucial importance of ventilatory distribution and alveolar air dilution becomes obvious. Here the mechanical event of lung inflation must also be considered from the functional perspective of, not only the mixing of the inspired air within the chamber of the lungs, but also the

manner in which perfusing pulmonary blood is exposed to the ventilated alveoli, thereby accomplishing the condition for the exchange of oxygen and carbon dioxide.

From a theoretical viewpoint, the physiological equivalence of natural and artificial ventilation of the lung depends in part upon the identity of air distribution. More precisely, correspondence should be sought in the relation of the quantity of alveolar ventilation to the quantity of blood perfusing the ventilated alveoli. Thus, if the effective alveolar ventilation and pulmonary blood perfusion ratios were found to be comparable, one would expect that the uptake of oxygen and the elimination of carbon dioxide would be identical and that a true physiological equivalence would be established. It is suggested that such is the case, but it should not be presumed that this relationship is unequivocally established nor, indeed, that such equivalence exists during abnormal states. The manner in which artificial pressure breathing affects the compensatory adjustments of the circulation is far from clarification; for example, in the circumstance of increasing or decreasing oxygen demand and carbon dioxide elimination in accordance with altered metabolism.

At present there are insufficient data, and there is considerable difficulty in measuring total respiratory function with a precision that would allow identification of the differences in ventilation distribution achieved by different methods of producing identical tidal volumes. It is reasonable to assume that there are alterations in the spatial distribution of air introduced into the lungs by applied pressure on the one hand, or by diaphragmatic action on the other. There is little doubt that natural and artificial respiration affect thoracic venous return in an opposite manner.[29, 30] The interference with thoracic venous return during artificial respiration is accentuated in conditions where vasomotor compensation leading to elevated venous pressure is ineffective or absent. In this circumstance it is possible that there are quantitative differences in lung blood volume, as there is undoubtedly a diminution in cardiac output. The influence of these changes upon pulmonary blood perfusion is probable, but has not been established. Recently Luft[31] has shown that the technique of rapid analysis of expired nitrogen is of real value in estimating the physiological dead-space dilution equivalent of pulmonary ventilation. This method, when applied to the use of artificial respiration, may clarify comparisons of ventilation distribution.

That these considerations may be of more theoretical than practical importance is suggested by Whittenberger: "Artificial and natural respiration are alike in basic-mechanical events . . . Modification of this statement may be necessary in cases of distribution of ventilation within the lungs, since the spatial displacement of thoracic boundaries is probably different when natural breathing is compared with most forms of artificial respiration. Such differences, if found, are undoubtedly of more theoretical than practical interest."[32] It is the opinion of the author that exceptions may be encountered, not only when there are extreme alterations of the mechanical behavior of the lungs, but also when there are disturbances in

pulmonary and systemic circulation. The latter may occur when the neurogenic regulation of these functions is disturbed as a result of brainstem disease or the action of pharmacological agents upon its integrative function.

Although the influence of the rate of emptying and filling of the physiological dead space upon alveolar ventilation is often unappreciated, it is of considerable practical importance in ventilation dilution. FIGURE 12 illustrates the relationship of minute volume at different rates of breathing to constant alveolar ventilation. In this calculation a constant R.Q. of 0.8 and a constant physiological dead space at different rates were assumed. The constancy of the physiological dead space is in dispute at present. The data were plotted from calculations made from the Radford nomogram for predicting the level of tidal ventilation necessary during artificial respiration according to various body weights and different rates of breathing.[33] It is apparent that if the rate of breathing is increased from 10 per minute to 40 per minute, the minute volume must be doubled in order to achieve the same degree of alveolar ventilation. Clearly, the minute volumes achieved at high rates of breathing are not equivalent in terms of alveolar ventilation to the minute volumes achieved at low rates. This finding should be considered in the choice of suitable rates for elective artificial respiration during anesthesia.

The Relationship of Artificial Respiration to the Biochemical Regulation of Oxygen and Carbon Dioxide

In view of the fact that the most rudimentary requirement of any artificial respiratory procedure utilized by the anesthesiologist is that it must

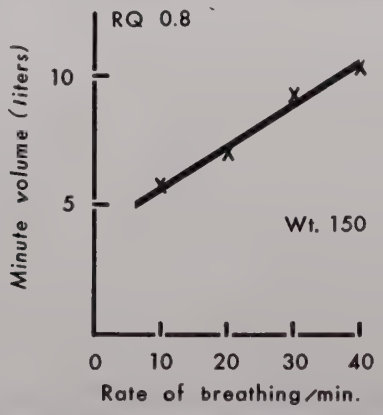

FIGURE 12. Relationship of different rates of breathing to the volume of ventilation per minute necessary to achieve constant alveolar ventilation. The increasing magnitude of the rate of emptying and filling of the dead space at high rates of breathing is indicated in the rising minute volume requirement. Values indicated by crosses were calculated from predicted tidal volume at different rates on the same hypothetical subject with body weight of 150 lb. A constant R.Q. of 0.8 and a constant dead space are assumed. (Calculations are made from the Radford nomogram.)

meet the metabolic requirement of oxygen uptake and carbon dioxide elimination, it is useful to investigate the manner in which this requisite is achieved. It may then be possible to define from a biochemical point of view the manner in which optimum ventilation can be attained for the patient undergoing anesthesia and artificial respiration.

During artificial respiration, as during natural breathing, the chemical requirements are satisfied by a critically regulated dilution of the atmosphere of the lungs with gas mixtures containing a higher partial pressure of oxygen and a lower partial pressure of carbon dioxide than those existing in the alveoli at the onset of each breath. Here it is important to recognize that, at the level of the alveolar membrane, respiration and circulation are united. Since the rapidly obtained equilibrations of oxygen and carbon dioxide (0.3 to 0.4 sec.) between alveolar air and pulmonary capillary blood obey the laws of gaseous diffusion, the area of alveolar membrane exposed to the pulmonary circulation and the pressure gradients of these gases across the alveolar surface are of major importance. Furthermore, the diffusion characteristics of the individual gases determine the pressure gradients at which equivalent volumes of the respective gases are exchanged. Adjustments for changing requirements of oxygen uptake and carbon dioxide elimination involve regulation of the volume of alveolar ventilation per unit time and, to some extent, alteration of the volume of pulmonary capillary blood exposed to the ventilated alveoli. On this basis, satisfaction of the requirements of gas exchange during artificial respiration consists, most simply, of regulating the dilution of air in the lungs to a degree approximating that of natural breathing, provided that the magnitude of the pressure gradients for diffusion approaches that of natural breathing. Clearly, the quantity of alveolar ventilation should approximate that of normal ventilation if the gas concentrations approach those of room air *and* if there are normal ventilation-distribution and blood-perfusion relationships. Similarly, severe alterations of general metabolism are presumed to be absent.

It is possible to demonstrate crudely the manner in which artificial pulmonary ventilation directly affects the ratio of oxygen consumption to carbon dioxide elimination. Figures 13, 14, and 15 illustrate this relationship under conditions of constant oxygen utilization and carbon dioxide production. Here the effect of ventilatory regulation in its elemental form may be seen. Figure 13 illustrates the relationship of oxygen uptake to increasing ventilation, during tank respiration, in healthy relaxed subjects in a steady state. Predicted "normal" levels of ventilation were chosen as starting points for each of 6 subjects. Oxygen consumption and carbon dioxide elimination approximated that of the subjects in the steady state prior to the institution of artificial respiration. The volume of ventilation per minute was adjusted by suitable increases in respirator pressure. The rate of cycling was held constant and was the minimum value that could be obtained in the respirator. Increases in the depth of tidal ventilation yielded minute volumes of 5 to 28 liters. In this example it is clear that there

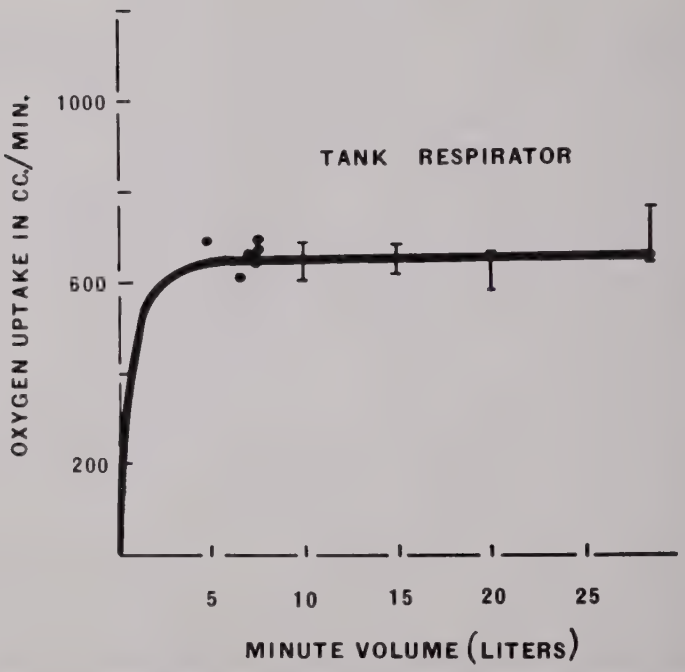

FIGURE 13. Oxygen uptake as a function of increasing ventilation during artificial respiration. The relationship of oxygen uptake to increasing minute volume is indicated by the curve. All volume measurements are corrected to BTSPS. Six healthy male adult subjects in a steady state and with comparable body surface area (1.85 to 2.0 sq. m.) were trained to permit passive artificial respiration in the tank respirator. The rate of cycling was held constant at 13 per minute, and the depth of tidal ventilation was varied by pressure adjustments. Initial oxygen consumption measurements by closed-circuit spirometry with carbon dioxide absorption and with 100 per cent oxygen are indicated as the dots at levels of ventilation predicted from the Radford nomogram. Averages of several readings were used for the ventilation measurements, which were taken by closed-circuit spirometry and by open-circuit Douglas bag collection of expired air for volumetric and gas analysis, through low-resistance valving. The vertical lines indicate the complete range of variation of the measurements of oxygen consumption at any given minute volume in excess of the predicted initial volume settings.

was little significant change in oxygen uptake during breathing of 100 per cent oxygen. In 2 subjects, slightly higher oxygen consumptions at large minute volume were believed to be due to voluntary supplementation, as indicated by the altered slope of simultaneously determined pressure-volume curves.

On the other hand, FIGURE 14 indicates that the elimination of carbon dioxide was directly proportional to increasing ventilation. The subjects had comparable body surface-area measurements, within a variation of 10 per cent, and were tested in a steady, but not basal, state. There was no ap-

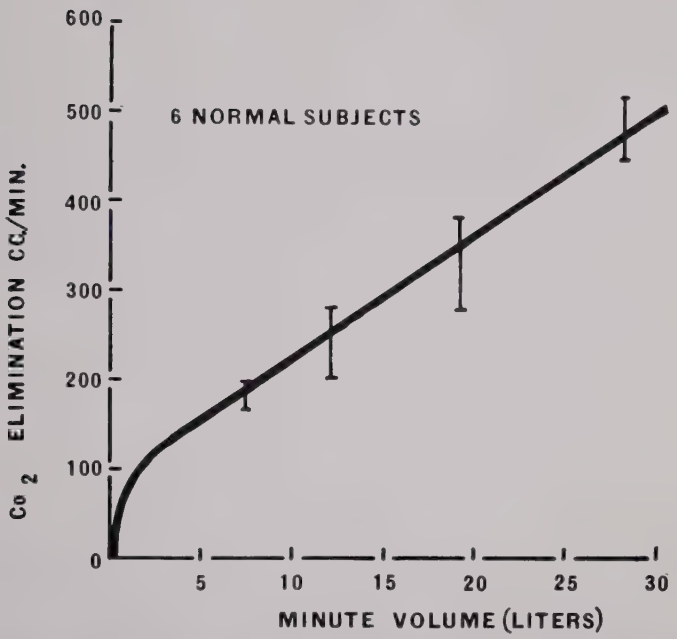

FIGURE 14. Carbon dioxide elimination as a function of increasing ventilation during artificial respiration. In this figure, the relationship of carbon dioxide elimination to increasing tank-respirator induced ventilation is indicated by the curve. All measurements corrected to BTSPS. The 6 subjects and the conditions of study were the same as described in FIGURE 13. Carbon dioxide elimination was determined by duplicate volume measurement and by analysis of representative 10-liter expired air collections when rapid infrared carbon dioxide analysis indicated the attainment of constant maximum expired P_{CO_2} levels after incremental increases in ventilation. Vertical lines indicate the range of individual curves at different levels of ventilation. Ventilation was increased from the respirator settings yielding predicted normal ventilation at the beginning of the experiment.

preciable change in body activity during the experiment. Increasing the ventilation increased the carbon dioxide elimination from 180 to 200 ml./min., to 500 ml./min. Ventilation was varied from 6 to 28 l./min. "Alveolar" carbon dioxide concentration was determined simultaneously; this variable is related to increasing ventilation in FIGURE 15. Carbon dioxide concentration in the terminal portion of the expired air was considered to represent alveolar concentrations. As ventilation was increased to 28 l./min., "alveolar" P_{CO_2} fell from control values of 35 to 40 mm. of mercury to levels of 15 to 20 mm. of mercury, and carbon dioxide elimination increased proportionately. Here again, the initial values indicated the suitability of predicted ventilation to approximate the normal range. On the basis of these data it is suggested that increasing the ventilation during artificial respiration affects the biochemical regulation of oxygen

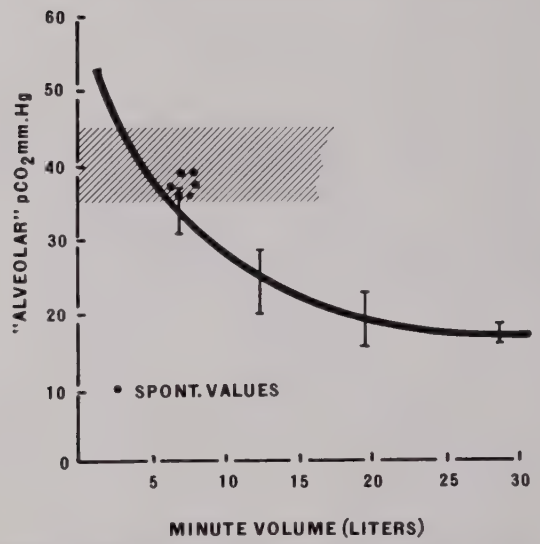

FIGURE 15. "Alveolar" carbon dioxide tension as a function of increasing ventilation during artificial respiration. The curve indicates the relationship of maximum expired carbon dioxide tension to increasing minute volume of ventilation during tank-respirator respiration in 6 healthy subjects. The subjects and conditions are the same as in FIGURES 13 and 14. The shaded area of the graph indicates the range of normal variation of the alveolar P_{CO_2} tension (35 to 45 mm. of mercury). The dots indicate the initial average P_{CO_2} tensions of the subjects at levels of ventilation predicted from the Radford nomogram. The vertical lines indicate the entire range of variation of the measurements on the separate subjects. Ventilation was increased from initial predicted normal levels in each case by respirator adjustments, and the representative P_{CO_2}'s were determined by infrared carbon dioxide analysis when the values became constant after incremental ventilation increased.

and carbon dioxide in a manner paralleling that in natural respiration of healthy subjects. The constancy of oxygen uptake is a consequence of the fact that the consumption of oxygen does not exceed its utilization, which remains constant (at the same partial pressure and total pressure), and that the progressively increased elimination of carbon dioxide is directly proportional to alveolar ventilation.

Prediction of Suitable Minute Volumes of Ventilation During Artificial Respiration

Under steady-state conditions the precise regulation of ventilation to obtain identical respiratory and metabolic respiratory quotients with room air breathing is a predictable phenomenon in healthy individuals. In this situation, alveolar-arterial P_{CO_2} tensions will be found to fall within the range of 35 to 45 mm. of mercury; arterial *p*H 7.35 to 7.45 units; and alveolar-arterial P_{O_2} tensions in the range of 95 to 105 mm. of mercury.

Oxygen saturation of the arterial blood will be above 95 per cent; oxygen uptake will be equivalent to metabolic utilization; and carbon dioxide elimination will preserve the metabolic respiratory quotient.

An ingenious application of this relationship is afforded in the Radford nomogram for predicting ventilation during artificial respiration.[33] FIGURE 16 is a reproduction of this nomogram. This useful device predicts the expected tidal ventilation at different rates of breathing and according to body weight and sex. A constant R.Q. of 0.8 is assumed, and there are suitable corrections for elevated body temperature, for activity, and for eating, as well as altitude corrections. As a starting point for levels of

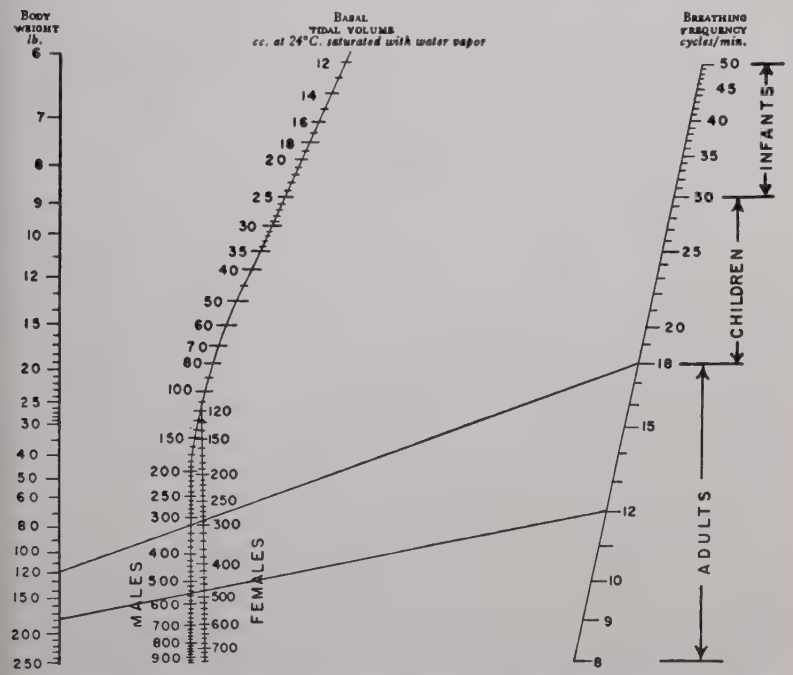

FIGURE 16. Radford nomogram for the prediction of tidal ventilation during artificial respiration according to body weight in pounds and rate of cycling. Appropriate straight lines connecting the breathing frequency of the respiratory device in cycles per minute with the body weight of the subject in pounds yield appropriate predicted tidal volumes in the middle graph. Males and females are indicated separately. Correction is made in the following manner: add 10 per cent for daily activity and eating; add 5 per cent for each degree of fever (F.°) above rectal normal of 99° F.; add 5 per cent for each 2000 ft. of residence above sea level; subtract an amount equal to one fourth of the body weight in pounds for the reduced anatomical dead space if the subject is breathing through a tracheotomy. (From Figure 1, "Clinical Use of a Nomogram to Estimate Proper Ventilation During Artificial Respiration," by E. P. Radford, Jr. *et al.* 1954. New England Journal of Medicine. Vol. 251, p. 22. Reproduced with permission of the author and publisher.)

artificially obtained pulmonary ventilation, it has been useful and reasonably accurate. In disease states such as poliomyelitis, values of 20 to 25 per cent larger appear to be necessary in the unsteady state of the acute phase of illness. Thereafter the lower values may be used if based upon pre-illness weight.

It should be stated that alterations of general metabolism and the effect of the changes in the respiratory system already discussed modify the suitability of the predicted values. For the unsteady state of anesthesia, it may be necessary slightly to increase the predicted values; in this sense, the nomogram provides minimum values.

Ideally, optimum ventilation involves steering a course between underventilation and hyperventilation that achieves the required gas exchange without calling forth or compromising the patient's protective or compensatory physiological responses. This must be done in a manner adaptable to anesthetic and surgical procedures. Obviously, detailed gasometric analysis and arterial blood analysis may be required whenever unsteady states or physiological disturbances are suspected.

It would be presumptuous to indicate that such a precise regulation of ventilation is more than an ideal at the present time. However, several practical suggestions are evident:

(1) At the very least, the level of pulmonary ventilation during artificial respiration should be measured and should not differ from predicted normal values. Exceptions may be encountered when oxygen utilization and carbon dioxide production are decreased, as may occur in hypothermic states or as a result of the action of hypometabolic drugs.

(2) Under most circumstances of near-normal ventilation-perfusion relationships in the lungs, terminal expired carbon dioxide tensions in the vicinity of 35 to 45 mm. of mercury should indicate adequate alveolar ventilation. Exceptions here may be the result of very shallow breathing in which adequate alveolar sampling cannot be assumed.

(3) Arterial oxygen unsaturation should be scrupulously avoided. Hypoxemia represents a very severe biochemical compromise, as judged by disturbances in brainstem respiratory and circulatory regulation. Similarly, retention of carbon dioxide should be avoided, since it leads to acidosis and requires considerable adjustment of extracellular and intracellular electrolyte distribution, together with renal excretory compensation.

(4) Rapid fluctuations of arterial carbon dioxide tension should be avoided, since they may promote central cardioregulatory abnormalities.[34] Hyperventilation alkalosis, in which such oscillations of P_{CO_2} develop, is a circumstance that is readily attained.

It should also be apparent that these requirements impose a considerable burden upon the anesthesiologist's judgment and accuracy of observation and upon the instrumentation available to him. Although the human being can tolerate remarkable physiological insults, it is obvious that surgical and anesthetic "trauma" should be kept at a minimum if the total trauma is to be reduced and the possibility of injury or death kept to an absolute mini-

mum, particularly in individuals with unsuspected or unmeasurable physiological deficiencies.

Factors involved in the comparison of artificial and natural respiration are summarized in TABLE 1.

Biochemical Dissociations Altering Ventilation Requirements During Artificial Respiration

Because the conditions of anesthetic practice and the status of the patient introduce factors that alter the direct applicability of the preceding defini-

TABLE 1

COMPARISON OF ARTIFICIAL RESPIRATION WITH NATURAL RESPIRATION

Points of comparison	Artificial respiration	Natural breathing
1. Basic mechanical event.	The application of pressure to produce a gradient across the pulmonary tissue, leading to air inflow and increased volume of the lungs and thorax.	The development of a pressure gradient across the pulmonary tissue, producing air inflow as a result of muscular contraction leading to enlargement of the thoracic compartment.
2. Volume equivalence of comparable pressure gradients.	. . . Identical . . .	
3. Variables in the regulation of pulmonary ventilation.	The magnitude of the applied pressure, the duration of average pressure, the mechanical behavior of the subject's lungs and thorax, the proportion of lung tissue subjected to the pressure gradient, and the mechanical characteristics of the respiratory device determine the magnitude of ventilation.	A continuously self-regulated process in which rate, depth, and pattern of breathing are efficiently adjusted to changing needs of cerebral, autonomic, and metabolic activity. Precise tailoring of the muscular work involved to the varying load of ventilation imposed by extremes of activity, disease, or injury.
4. Physiological equivalence of the same volume of ventilation.	. . . Probably similar in steady states . . .	
5. Ventilation distribution: blood perfusion relationships.	Not known precisely.	Under normal circumstances, "ideal" ventilation distribution: blood perfusion ratios, leading to equivalence of alveolar gas, pulmonary capillary blood O_2 and CO_2 tensions, and identical respiratory and metabolic R.Q.'s.
6. Circulatory effect of pulmonary ventilation.	Impairment of thoracic venous return proportional to mean pressure. In abnormal states of insufficient vasomotor compensation of elevated venous pressure, cardiac output is decreased.	Intrathoracic and intra-abdominal pressure gradients favor thoracic venous return; cardiac output cyclically increased during end inspiration.

tion of the ventilatory requirement, the presentation of additional considerations may be useful. The provision of alveolar ventilation volumetrically approximating that of natural breathing if the gas concentrations approach that of room air may not be the usual situation in the artificial respiration used in anesthesia.

From a theoretical standpoint, and in view of scattered observations made during anesthesia and in poliomyelitis patients requiring artificial respiration, biochemical disturbances and abnormal mechanical behavior that may alter the applicability of the foregoing analysis of ventilatory requirements include: (1) increasing or decreasing cellular oxygen metabolism as a chemical effect of anesthetic and preanesthetic medication; (2) alterations of ventilation distribution to blood perfusion relationships as a result of nonuniform expansion of the lungs or as a consequence of the unsuitability of responses of the systemic or pulmonary circulation; (3) reduction in the net volume of functioning lung tissue due to obstructing bronchial secretions, alveolar fluid barriers, or the restricted pulmonary expansion encountered in some thoracic and abdominal procedures; and (4) the ineffectiveness of anesthetic equipment to regulate the carbon dioxide concentration of the inspired air in rapid breathing with closed-circuit techniques.

The consequences of such disturbances may include:

(1) Simple underventilation in which hypoxemia, hypoxia, and retention of carbon dioxide develop, with eventual appearance of respiratory acidosis if the arterial *p*H declines below 7.35 units.

(2) Underventilation with high partial pressure of inspired oxygen, leading to carbon dioxide retention without hypoxemia or hypoxia. The high oxygen tensions used in ordinary anesthesia may mask the development of underventilation, since there will be adequate diffusion pressure for oxygen uptake and thus the usual coexistent signs and symptoms of hypoxemia fail to develop with the carbon dioxide retention.

(3) In the presence of "normal" levels of ventilation and room-air oxygen tension, high oxygen utilization or reduced functioning lung tissue or unequal ventilation distribution leads to hypoxemia without carbon dioxide retention. In this instance, the more favorable diffusion characteristics of carbon dioxide and the relative overventilation in some areas of the lung prevent carbon dioxide retention. Extremely severe disturbances of distribution of ventilation and shunting of blood away from overventilated areas of the lungs, together with reduced carbon dioxide production, may lead to hypoxemia with hyperventilation hypocapnia.

I have no firsthand experience of the extent to which these possibilities are germane to artificial respiration during anesthesia and shall present only what has been reported in the recent literature. Elam and Brown[35] have pointed out disturbances in the homeostasis of carbon dioxide during anesthesia as a consequence of insufficient carbon dioxide absorption during closed-circuit artificial respiration and as a result of metabolic disturbances during anesthesia. These authors emphasize the fact that, in their experience, ether anesthesia appears to increase both oxygen consumption and

carbon dioxide production. On the other hand, general metabolism is reduced after administration of some other anesthetic agents, such as the barbiturate derivatives.

It is also worthwhile to suggest that abnormal body positions, open-chest surgery, and controlled atelectasis for surgical exposure may alter pulmonary ventilation distribution and pulmonary circulation. Furthermore, the effects of pressure breathing upon the systemic circulation and the influence of central "depressant" drugs upon cardiac and vasomotor regulation may be of critical significance in prolonged anesthesia.

The occurrence of severe biochemical dissociations during artificial respiration in severe bulbospinal poliomyelitis is indicated in FIGURE 17. The patient, who had extensive respiratory muscle paralysis requiring artificial respiration, was studied in a serial manner. The opportunity was provided to compare tank-respirator ventilation and chest-abdomen cuirass ventilation in an acute phase of illness in which ventilation exceeding predicted levels appeared to be inadequate from the point of view of regulation of oxygen and of carbon dioxide. At the time of study there was no radiographic evidence of pneumonitis or atelectasis. There were cardioregulatory disturbances, and there was suggestive evidence in the serial electrocardiogram, in the chest radiograph, and in cardiac measurements for myocarditis and pulmonary congestion. In the first set of ventilatory and femoral arterial chemical measurements, it is clear that arterial hemoglobin unsaturation (88 per cent) occurred at relatively high levels of minute volume ventilation, exceeding predicted ranges (indicated in the horizontal shaded area). Slight alkalosis is indicated by the arterial *p*H of 7.47 units, and the arterial P_{CO_2} tensions, in the range of 27 mm. of mercury, are consistent with hyperventilation. Tidal volume was within the normal range of 500 ml., and the rate of respiration was 20 cycles per minute. High pressure settings of 28 to 30 cm. of water were necessary to achieve this depth of breathing. Minute volume was found to be 10.0 liters. The patient was inhaling room-air concentrations of oxygen with the addition of 100 per cent humidified oxygen by open delivery to the tracheotomy airway. Higher rates of breathing appeared to be inadvisable because preliminary studies of airflow pressure-volume relationships indicated increased air-inflow resistance. Without changing the pressure setting of the respirator, 100 per cent oxygen was delivered through a closed-circuit rebreathing spirometer with carbon dioxide absorption. Infrared monitoring of the concentration of inspired and expired carbon dioxide indicated adequate absorption.

The effect of the addition of 100 per cent oxygen can be seen in the second set of measurements. Tidal volume increased in depth to 600 ml., and the corresponding minute volume increased to 12.0 liters. Coincident with this, arterial P_{CO_2} decreased further to 25 mm. of mercury, and oxygen consumption increased from 190 to 320 ml./min. Oxygen saturation increased to 95 per cent, and the arterial *p*H declined paradoxically to 7.43 units. With elevation of oxygen saturation to normal values, the pressure-volume

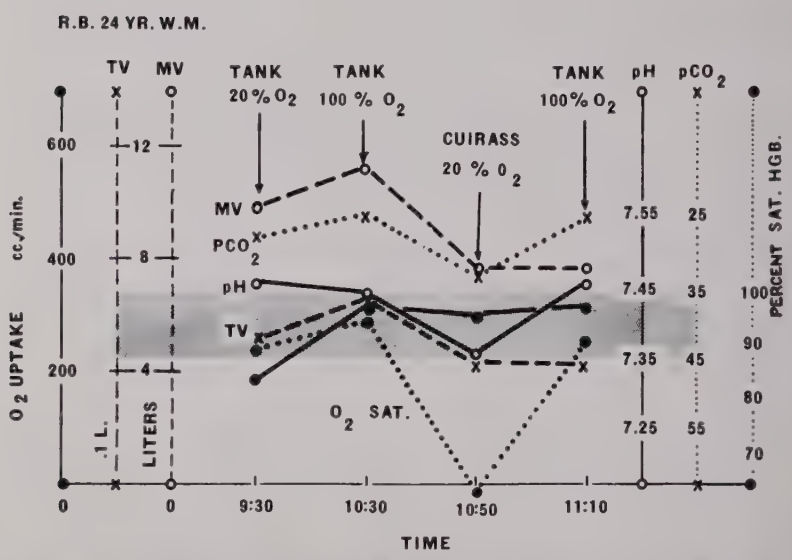

FIGURE 17. Respiratory function during artificial respiration in a subject with acute bulbospinal poliomyelitis. This figure illustrates the response of 6 indices of respiratory function during tank-respirator and cuirass-respirator pulmonary ventilation. The subject had acute bulbospinal poliomyelitis, and extensive respiratory muscle and extremity muscle flaccid paralysis. Hypotension, myocarditis, pulmonary congestion, cardioregulatory disturbances of bradycardia, present in association with paralysis of the swallowing musculature, were indicative of brainstem disease. To the left of the figure the vertical dimension indicates, from left to right, oxygen uptake in cc./min., tidal volume in 0.1 liters, and minute volume in liters (corrected). The right-hand vertical dimension indicates arterial blood pH, P_{CO_2} tension in mm. of mercury, and percentage saturation of hemoglobin, calculated from capacity and oxygen content of the arterial blood. From the top downward, serial measurements indicated by dashed, dotted, and solid lines are: minute volume, P_{CO_2}, arterial pH, tidal volume, per cent oxygen saturation, and oxygen uptake. The first set of measurements was made during the most steady condition of the patient. Tank respiration was carried out at a pressure of — 28 cm. of water and a cycling rate of 20. Room air with humidified oxygen supplement in an open system was being delivered to a no. 6 tracheotomy tube. Measurements were made through the tracheotomy tube with the mouth and nose occluded. The second set of measurements differs by virtue of the addition of 100 per cent oxygen alone in a closed-system spirometer. The third set of measurements, characterized by a marked decrease in oxygen saturation, was made during chest-abdomen cuirass respiration. The last set of measurements was made with the patient back in the tank respirator with the same settings of rate and pressure as before, and inhaling 100 per cent oxygen through a closed-circuit spirometer. The horizontal dimension indicates the time scale. Volumetric measurements indicate the diminution in tidal exchange that occurred during chest-abdomen cuirass respiration, which was sustained when tank respiration was reinstituted. Different arterial chemistries are indicated also in the comparison of the last two sets of measurements, in spite of identical tidal and minute volume values. The shaded area indicates the range of predicted normal tidal ventilation and minute volume for the body weight and temperature of the patient. On the right, the shaded area includes that portion of the vertical pH and P_{CO_2} scale that may be considered to include normal variation.

characteristics of the patient had improved. Airflow pressure studies at this time indicated a diminution in air-inflow resistance.

In the third set of measurements the chest-abdomen cuirass respirator was utilized, and tidal ventilation declined from 600 ml. to 400 ml. (at −35 cm. of intrashell peak pressure). With 20 per cent inspired oxygen concentration, oxygen consumption remained the same when measured, with careful preservation of room-air concentrations, in the spirometer bell by the calibrated addition of amounts of 100 per cent oxygen equal to consumption. Arterial oxygen saturation declined to the very low value of 65 per cent; serial electrocardiograms indicated the development of bradycardia and changes in the configuration of the P wave; blood pressure decreased to 90 mm. of mercury (systolic). Arterial P_{CO_2} increased to 33 mm. of mercury, and arterial pH decreased to 7.35 units.

Because of rapid deterioration of the patient's circulatory status with this hypoxemic episode, tank-respirator respiration was reinstituted at the same pressure and rate as before and with closed-circuit delivery of 100 per cent oxygen in the inspired air. The fourth set of measurements indicates that the values of tidal volume and minute volume obtained with the tank respirator corresponded to those obtained in the cuirass and were now less than had been previously achieved with the tank. Oxygen saturation rose to 92 per cent, the arterial P_{CO_2} decreased again to 25 mm. of mercury, and the pH shifted back to the alkaline range of 7.47 units. Thus, the same degree of pulmonary ventilation, as measured by tidal and minute volume, was associated with entirely different arterial chemical measurements in the tank respirator as compared with the cuirass respirator. Hypoxemia coexisted with hyperventilation and slight arterial alkalosis. Although the existence of disturbances of ventilation distribution and alterations of pulmonary blood perfusion is presumptive, it is clear that the estimation of optimal ventilation for biochemical homeostasis was not provided in conventional ventilatory predictions. Steady-state assumptions did not adequately describe optimum ventilation unless correction, based upon arterial chemical studies, of either volume or inspired gas concentrations was made. It is not known to what degree similar dissociations may occur in general anesthesia with artificial respiration in conditions in which severe disturbances in respiratory behavior may develop.

Figures 18 and 19 (from Huggins *et al.*[6]) illustrate another aspect of the problem of assessing the physiological equivalence of pulmonary ventilation in terms of a single parameter of respiratory function. In these examples the respiratory effect of morphine and *N*-allylnormorphine, both of which act centrally, was investigated in a group of 16 postoperative convalescent "normal" subjects. Both drugs were administered intravenously, separately and in combination (*N*-allylnormorphine following morphine), in doses comparable to their relative potency. The 2 drugs separately produced severe and comparable levels of depression of spontaneous tidal ventilation, of minute volume of breathing, and of calculated alveolar ventilation (not shown). A periodicity of respiratory pattern was evident

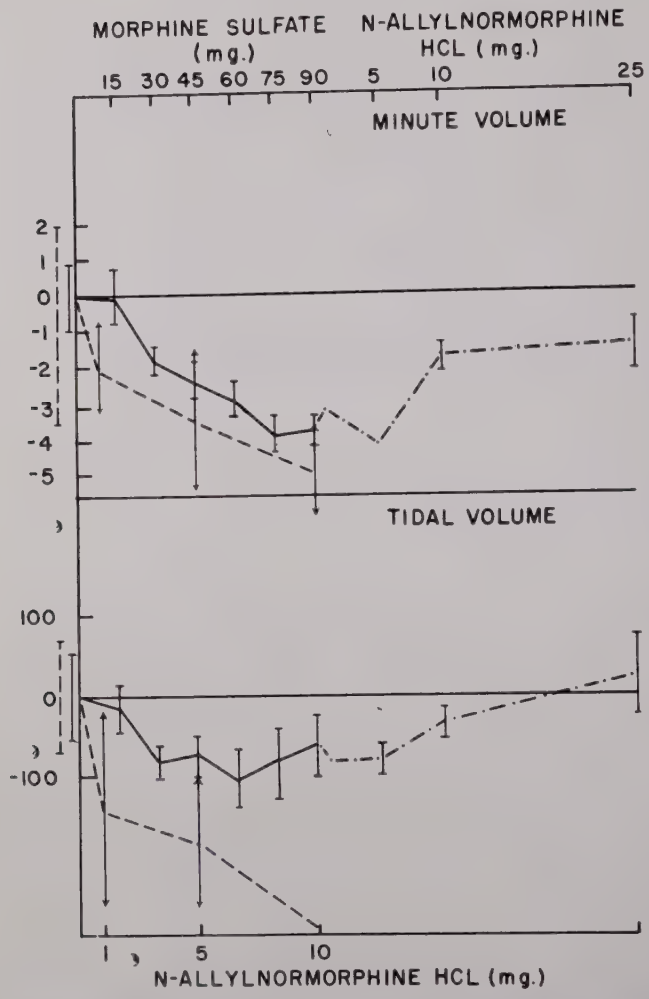

FIGURE 18. Effect of morphine and *N*-allylnormorphine on spontaneous ventilation in human subjects. In FIGURES 18 and 19, the effect of intravenous morphine alone is represented by the solid line, of *N*-allylnormorphine by the dashed line, and of *N*-allylnormorphine after 90 mg. of morphine by the dashed-dotted line to the right of the morphine line. The effect of successive doses of morphine up to 90 mg. and of *N*-allylnormorphine up to 10 mg. when administered alone, and of 25 mg. when given after 90 mg. of morphine, upon the minute volume is indicated in the top figure, and upon the tidal volume in the lower figure. The drugs were administered intravenously to 16 subjects convalescent from surgical operations. One standard error from the mean, in all cases where there were 5 to 16 measurements, is indicated by a vertical crossed line at the appropriate dosage of the drugs. The standard error for the control periods is on the left of the graph on the ordinate. The mean effect after 90 mg. of morphine was used as the control value for calculations of the subsequent responses to *N*-allylnormorphine. All vertical scales represent absolute mean changes from the mean control value. The vertical scale intervals for minute volume indicate a 10 per

cent change; the scale ordinate for tidal volume represents a 20 per cent change. (From "Respiratory functions in man following the intravenous administration of morphine, *N*-allylnormorphine, and *N*-allylnormorphine after morphine," by R. A. Huggins, W. A. Spencer, L. A. Geddes, S. Deavers, and J. H. Moyer. 1957. Submitted for publication. This figure and FIGURE 19 are reproduced, with permission from the authors, prior to publication elsewhere.)

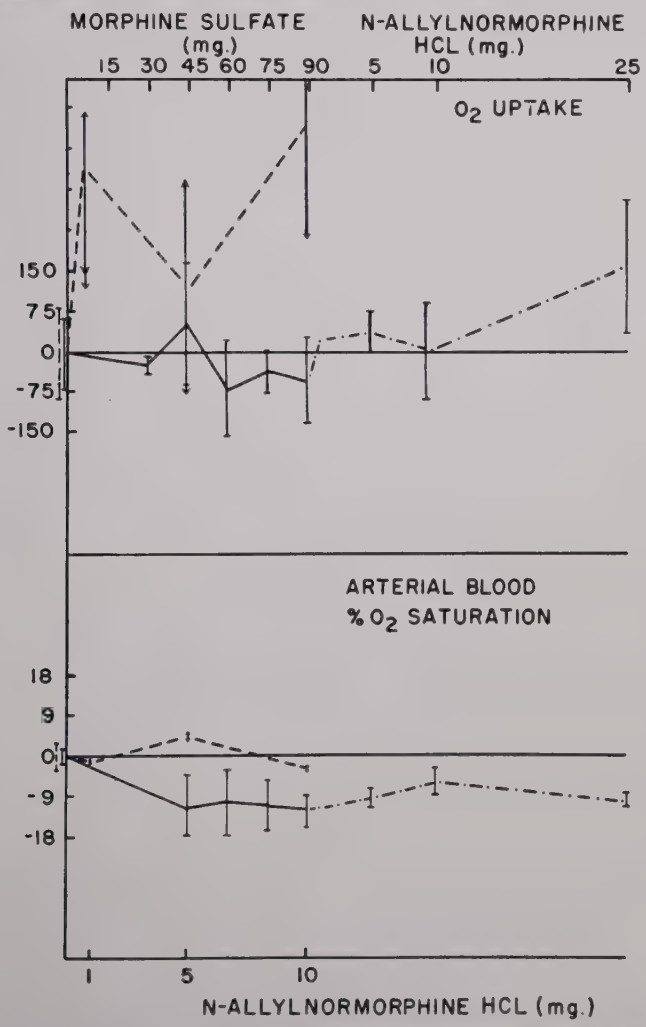

FIGURE 19. Effect of morphine and *N*-allylnormorphine on oxygen uptake and arterial blood percentage of oxygen saturation in human subjects. For a general description see FIGURE 18. FIGURE 19 illustrates the response to the underventilation induced by morphine and *N*-allylnormorphine alone and by *N*-allylnormorphine following 90 mg. of morphine. The ordinate scale intervals for both oxygen uptake and arterial blood oxygen saturation represent a 10 per cent change.

with morphine, but not with *N*- allylnormorphine. FIGURE 19 shows clearly that morphine in a dosage range of 70 to 90 mg. induced underventilation and was associated with decreasing arterial oxygen saturation. Arterial oxygen content decreased in a similar manner, but this is not shown. There was no apparent change in oxygen uptake. On the other hand, *N*-allylnormorphine produced a similar degree of ventilatory depression but, under identical circumstances of measurement, did not produce depression of arterial oxygen saturation or of oxygen content (the latter is not shown). Furthermore, it is clear from this figure that there was a remarkable increase in oxygen consumption. The effects of these 2 drugs could not be evaluated adequately by tidal and minute volume measurements alone, as they have been conventionally studied in humans. The differences, while they are complex and concern spontaneous breathing, indicate that one cannot assume that a given depression of ventilation means the same extent of biochemical disturbance in the case of 2 drugs that directly affect the regulatory mechanism in the central nervous system but have different effects on general cellular metabolism.

The preceding observations emphasize again the importance of both serial and multidimensional measurements. Without such measurements, the complex response of the human organism in unsteady states may defy interpretation.

The illustrations have been chosen to focus attention on the type of problem that may be encountered in the human subjected to prolonged artificial respiration during extensive surgery involving particularly the lungs and heart. In these individuals, insidious biochemical disturbances may not only alter the neuroregulatory mechanism sustaining vital functions, but may be summated with the effects of commonly employed pharmacological and anesthetic agents. In this sense, then, the anesthesiologist must assume the responsibility for physiological monitoring and investigation as surgical procedures increase in extent and his armamentarium is found to include procedures and drugs of widespread effect upon bodily function.

Conclusions and Summary

The foregoing synthesis of the factors of importance in controlled respiration suggests the following generalizations:

(1) Artificial and natural respiration are remarkably similar. They share basic mechanical events and differ principally in the precise manner in which neural genesis and regulation effect the co-ordinate activity most suited to the complete needs of the organism.

(2) The interplay and summation of the variables affecting pulmonary ventilation may resolve apparent or real differences in mechanical apparatus and in the ventilatory response of the patient.

(3) The anesthesiologist is not absolved from the responsibility of deciding when the patient's spontaneous breathing efforts are sufficient, because

the decision to utilize artificial respiration is elective and its discontinuance is not.

(4) It is essential to carry out quantitative measurement of pulmonary ventilation routinely if homeostasis of oxygen and carbon dioxide is to be achieved in the most elementary manner.

(5) Volumetric evaluation of respiratory sufficiency should be supplemented by more elaborate physiological and biochemical measurements in situations of extensive cardiopulmonary surgery, the prolonged use of artificial respiration, or the use of anesthetic agents and drugs that affect the central nervous system and general metabolism.

(6) From the physiologist's point of view, ideal anesthesia and artificial respiration should strive to minimize even tolerable physiological compromises in the effort to make the practice of anesthesia a minimum risk for the patient.

(7) Ideally, continuous registration of respiratory, circulatory, and metabolic activities will be necessary to describe the course of physiological dissolution and the effectiveness of corrective or compensatory procedures employed in the course of extensive surgery; in the use of synthetic heart and lung organs; and as a result of the survival of severely injured or diseased patients.

A more complete understanding of the physiological impact of surgery, of anesthesia, and of the administration of pharmacological agents awaits more extensive and elaborate documentation than is now available. Clearly, empirical and experimental observations must be recorded and quantitated if either the significance or the limitations of such experiences are to find proper meaning and usefulness.

Acknowledgments

This paper was prepared with the assistance of Robert R. Jackson, Carlos Vallbona, and Gunyon M. Harrison and with the technical assistance of Billye Bailey, of the Departments of Physiology and Pediatrics, Baylor University College of Medicine, and the Southwestern Poliomyelitis Respiratory and Rehabilitation Center, Jefferson Davis Hospital, both in Houston, Texas. The Center is supported by an annual grant-in-aid from The National Foundation for Infantile Paralysis, Inc.

References

1. Hoff, H. E. & C. G. Breckenridge. 1952. J. Neurophysiol. **15**: 47.
2. Breckenridge, C. G. & H. E. Hoff. 1952. J. Neurophysiol. **15**: 57.
3. Breckenridge, C. G. & H. E. Hoff. 1953. Arch. intern. pharmacodynamie. **93**: 1.
4. Hoff, H. E., & C. G. Breckenridge. 1955. *In* Textbook of Physiology: 843–865 & 867–886. John F. Fulton, Ed. W. B. Saunders. Philadelphia, Pa.
5. Southwestern Poliomyelitis Respiratory Center. 1954. Annual Respiratory Centers Conference on Physiologic Problems in Poliomyelitis, Boca Raton, Fla. Sponsored by Nat. Foundation for Infantile Paralysis, Inc. Unpublished.
6. Huggins, R. A., W. A. Spencer, L. A. Geddes, S. Deavers & J. H. Moyer. 1957. Arch. intern. pharmacodynamie. In press.
7. Hoff, H. E. Personal communication.

8. Hoff, H. E., C. G. Breckenridge & W. A. Spencer. 1952. Am. J. Physiol. **171**(1): 178–188.
9. Comroe, J. H., Jr., R. E. Forster, A. B. DuBois, W. A. Briscoe & E. Carlsen. 1955. The Lung: 42. Year Book Publ., Inc. Chicago, Ill.
10. Grodins, F. S. 1950. Physiol. Revs. **30**: 222–329.
11. Gray, J. S. 1949. Pulmonary Ventilation and Its Physiological Regulation. Charles C. Thomas. Springfield, Ill.
12. Hesser, C. M. 1949. Acta Physiol. Scand. **18**(64): 346–425.
13. Bjurstedt, A. G. H. 1946. Acta Physiol. Scand. **12**(38): 1.
14. Winterstein, H. 1955. Ergeb. Physiol. biol. Chem. u. exptl. Pharmakol. **48**: 1.
15. Rohrer, F. 1925. Handb. norm. u. pathol. Physiol. **2**: 70.
16. Rohrer, F. 1915. Pflügers Arch. ges. Physiol. **162**: 225–229.
17. Neergaard, K. V. & K. Wirz. 1927. Z. klin. Med. **105**: 35.
18. Otis, A. B., W. O. Fenn & H. Rahn. 1950. J. Appl. Physiol. **2**: 592.
19. Mead, J. & J. L. Whittenberger. 1953. J. Appl. Physiol. **5**: 779.
20. Whittenberger, J. L. Personal communication.
21. Rahn, H., A. B. Otis, A. E. Chadwick & W. O. Fenn. 1946. Am. J. Physiol. **146**: 161.
22. Day, R., A. M. Goodfellow, V. Apgar & G. J. Beck. 1952. Pediatrics. **10**: 593.
23. Fenn, W. O. 1951. Am. J. Med. **10**: 77–90.
24. Ferris, B. G., J. Mead, J. L. Whittenberger & G. A. Saxton, Jr. 1952. New Engl. J. Med. **247**(11): 390–393.
25. Southwestern Poliomyelitis Respiratory and Rehabilitation Center. Unpublished data.
26. Nims, R. G., E. H. Conner & J. H. Comroe, Jr. 1955. J. Clin. Invest. **34**: 744.
27. Spencer, W. A. 1956. Treatment of Acute Poliomyelitis: 179. Charles C. Thomas. Springfield, Ill.
28. Collier, C. R. & J. E. Affeldt. 1954. J. Appl. Physiol. **6**: 531–538.
29. Cournand, A., H. L. Motley, L. Werko & D. W. Richards, Jr. 1948. Am. J. Physiol. **152**: 162–174.
30. Maloney, J. V., Jr., J. O. Elam, S. W. Handford, G. A. Balla, D. W. Eastwood, E. S. Brown & R. H. Ten Pas. 1953. J. Am. Med. Assoc. **152**: 212–216.
31. Luft, U. C., E. H. Roorback & R E. MacQuigg. 1955. Am. Rev. Tuber. & Pulmonary Diseases. **72**: 4.
32. Whittenberger, J. L. 1955. Physiol. Revs. **35**(3): 611–625.
33. Radford, E. P., Jr., B. G. Ferris & B. C. Kriete. 1954. New Engl. J. Med. **251**: 22.
34. Brown, E. B., Jr. & F. A. Miller. 1952. Am. J. Physiol. **169**: 56.
35. Elam, J. O. & E. B. Brown, Jr. 1955. Anesthesiology. **16**(6): 868–902.

THE DIRECT EFFECTS OF PRESSURE BREATHING ON THE PULMONARY CIRCULATION

By James V. Maloney, Jr.
University of California Medical Center at Los Angeles, Los Angeles, Calif.
and
James L. Whittenberger
Harvard School of Public Health, Boston, Mass.

The effects of pressure breathing on the systemic and pulmonary circulations are of practical concern to the anesthesiologist because the technique of controlled respiration is so commonly employed. During World War II the contributions of physiologists interested in aviation medicine added greatly to our knowledge of the effects of positive airway pressure on the systemic circulation. The present discussion is concerned with a less well understood aspect of the problem: the direct effects of pressure breathing on the blood vessels within the lungs.

Pressure Breathing and the Systemic Circulation

Stimulated by problems of military medicine during World War II, many investigators studied the effects of pressure breathing on the normal individual. An excellent review of this research was published by Barach, Fenn, Ferris, and Schmidt.[1] The effects of moderate positive airway pressures on the systemic circulation of the normal individual may be summarized as follows: (1) Cardiac output remains the same, or shows, at most, a fall of about 15 per cent; (2) venous pressure rises; (3) peripheral vascular resistance increases; (4) arterial pressure rises as the result of vasoconstriction, a maintained cardiac output, and an increased base-line pressure within the thorax; (5) blood is displaced from the thorax to the peripheral venous bed; and (6) blood volume falls slightly.

Despite the fact that the foregoing changes seemed rather inconsequential, there continued to be reports,[2–4] as there had been for many decades, that positive pressure in the experimental animal might have deleterious effects on the circulation. The disparity between these 2 groups of observations was explicable when one observed that pressure breathing was tested under different conditions by the 2 groups of investigators. The normal subjects studied by the aviation physiologists only occasionally suffered circulatory collapse when subjected to 15 to 20 mm. Hg of continuous positive pressure. On the other hand, patients or animals suffering from barbiturate poisoning, hemorrhage, spinal anesthesia, or vasomotor paralysis regularly developed severe circulatory depression from relatively low levels of positive airway pressure. A clinical study performed on patients in various conditions of circulatory stress demonstrated that even the usual degrees of positive pressure employed in clinical practice may produce a profound depression of the systemic circulation.[5]

The application of these observations to the clinical practice of controlled respiration in anesthesia will be discussed subsequently.

Pressure Breathing and the Pulmonary Circulation

It has been much more difficult to understand the effects of airway pressure on the pulmonary circulation. Some of the confusion arises from the fact that the systemic effects of pressure breathing in certain clinical conditions are often mistaken for direct pulmonary effects. For example, it has been clinically observed that pressure breathing is of value in the treatment of pulmonary edema. Without experimental justification, this benefit is usually attributed to the effect of the increased alveolar pressure in "forcing" fluids back across the pulmonary capillary membrane. The increased alveolar pressure is visualized as affecting the Starling capillary equilibrium and preventing the transudation of fluid. Little cognizance is taken of the fact that positive airway pressure displaces blood from the lungs and heart, may diminish venous return and cardiac output, and causes a reduction in blood volume. The latter changes offer a rational explanation of any benefit that may be derived from pressure breathing in the treatment of pulmonary edema .

The most cogent deterrent to an understanding of the direct effects of pressure breathing on the pulmonary circulation has been the lack of objectivity with which we, as physicians, ordinarily think about the mechanics of respiration. In normal respiration, the lung is generally and erroneously believed to be expanded by the increase in negative pleural pressure around the lung. In apparent contrast, we think of controlled respiration as expanding the lung by the action of the increased pressure from within the alveolus. Such a proposition is unacceptable to the physicist, who is unwilling to admit that a "negative pressure" is capable of expanding anything. The physicist defines negative pressure as a pressure that is less than some other pressure that is arbitrarily chosen as a base line for reference. The physicist will point out that, in normal respiration, atmospheric pressure acting via the tracheobronchial tree is responsible for expansion of the lungs. It is apparent that, in both normal and positive-pressure breathing, the force causing lung expansion is an excess of pressure within the lung compared to the pressure on the external surface of the lung.

In view of these considerations, one might anticipate the results of the following experiments that were designed to compare the direct pulmonary effects of normal and positive-pressure lung inflation. The direct effects of the 2 methods of breathing on the pulmonary circulation must be the same.

Experimental Method

Experiments were performed on a group of 5 dogs to study the relationships among alveolar pressure, pulmonary "capillary" pressure, and pleural pressure during inflation of the lung by normal inspiration and by positive-

pressure inspiration. After the animal was anesthetized, arrangements were made for recording a number of physiological variables. The experiment is illustrated diagrammatically in FIGURE 1. By means of an endotracheal tube, the animal was connected to a to-and-fro carbon dioxide absorbing system. Positive-pressure breathing could be produced by squeezing the anesthesia bag attached to the cannister. An electrophrenic respirator[4] was attached to both phrenic nerves so that a normal type of inspiration of any desired depth or duration could be induced electrically. A differential pneumotachograph was inserted in the airway to record airflow. Pressure in the pulmonary system was measured by a pressure transducer inserted in the airway at the end of the endotracheal tube. By means of the pressure transducer and the pneumotachograph, alveolar pressure could be measured since, at times of zero airflow, pressure recorded at the mouth was equilibrated with pressure in the pulmonary alveoli. A cardiac catheter was advanced through the venous system to the pulmonary artery, where it was lodged firmly in a small arterial branch to measure

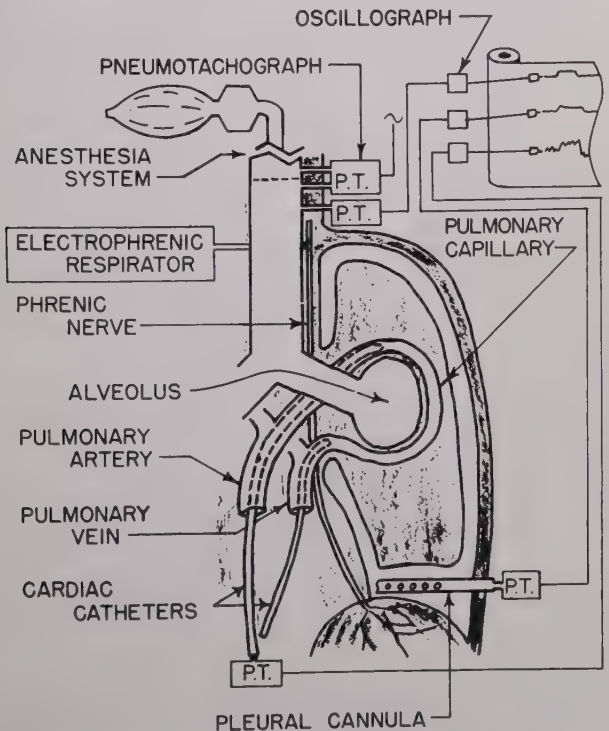

FIGURE 1. Diagrammatic presentation of experiment. "P.T." indicates pressure transducers.

pulmonary "capillary" pressure. In some experiments a second catheter was introduced retrograde through the arterial system and left ventricle to lie free in a pulmonary vein. A multiperforated pleural cannula was inserted so that it communicated with both pleural spaces. Airway and pleural pressures were related to ambient atmospheric pressure. Pressures measured from the cardiac catheters were related to an arbitrary external zero point (skin of the animal's back). All pressures were recorded simultaneously on a multichannel direct-writing oscillograph.

Observations

FIGURE 2 shows the changes that occur in airway, pleural, and pulmonary "capillary" pressures during a prolonged "normal" inspiration, and during a prolonged positive-pressure inspiration. On first inspection, it appears that the 2 types of inspiration have diametrically opposite effects. However, a brief consideration indicates that comparison of the pressures as illustrated in FIGURE 2 introduces a systematic error into the experiment: that is, the

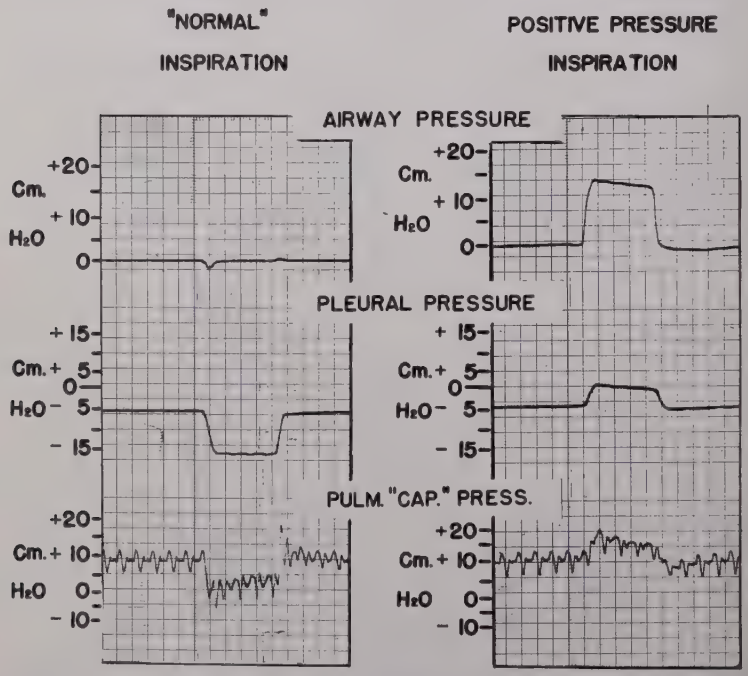

FIGURE 2. Comparison of normal and positive pressure inspiration. Base line for airway and pleural pressures is ambient atmospheric pressure. Base line for pulmonary capillary pressures is an arbitrary external zero point.

pressures are measured in relation to an arbitrary external zero point, rather than to one another. Since we seek the relationship among the 3 pressures within the chest (alveolar pressure, pulmonary "capillary" pressure, and pleural pressure), we must measure them in relation to one another. One pressure must be chosen as a base line and the other two pressures measured with reference to it. This could be done by employing differential manometers to measure, for example, airway and pulmonary "capillary" pressures in relation to pleural pressure used as a base line. Alternatively, the pressures can be measured as described above and then replotted, employing one of the pressures as a base line.

An analogy would perhaps be helpful in illustrating this transposition. Let us suppose that a man is placed within a pressure chamber and that his blood pressure is then measured through a column of saline attached to a transducer located outside the chamber. The ambient pressure within and without the chamber is the same, and the man's blood pressure will measure 120 mm. Hg in excess of both. When the pressure in the chamber is increased by 100 mm. Hg, the man's blood pressure will still remain 120 mm. Hg greater than the ambient pressure within the tank. As measured by the transducer located outside the tank, his blood pressure will equal 120 mm. Hg plus the 100 mm. Hg pressure change that has taken place within the tank (that is, 220 mm. Hg). Under such circumstances, it is always necessary to measure physiological pressures in relation to the pertinent zero base line. So it is with the experiments described above.

FIGURE 3 shows pleural and pulmonary "capillary" pressures replotted by point-to-point analysis related to airway pressure taken as the base line. It is immediately apparent that changes in pleural and pulmonary "capillary" pressures with normal inspiration and with positive-pressure inspiration are the same. The illustration of these pressure relationships in FIGURE 3 is perhaps unnecessary, since to the physicist this relationship is axiomatic.

One minor difference between the 2 types of inflation (FIGURE 3) reflects changes in the systemic circulation. It is noted that as the normal inspiration is initiated and sustained, pulmonary "capillary" pressure rises slowly. This is due to the increased venous return and the increased output of the right ventricle resulting from the prolongation of negative pleural pressure. In contrast, pulmonary "capillary" pressure during positive-pressure inspiration falls slightly during the time that the positive pressure is held on the airway. This decline in pulmonary "capillary" pressure reflects a decreased venous return and decreased output of the right ventricle. These are changes secondary to the effects of respiration on the systemic circulation, and do not represent direct pulmonary effects of pressure breathing.

Discussion

The foregoing experiment does not attempt to quantify the effects on a number of important variables that occur with changes in lung volume (for example, pulmonary vascular resistance, pulmonary blood volume, and

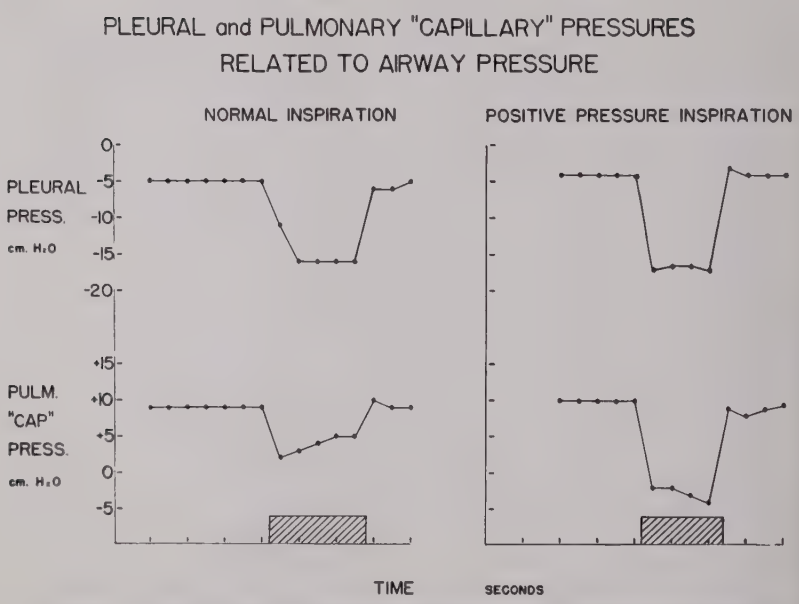

FIGURE 3. Replot of data in FIGURE 2 employing airway pressure as zero base line for pleural and pulmonary "capillary" pressures.

bronchial diameter). The experiment does indicate, however, that the direct effects of a positive-pressure inspiration on the pulmonary circulation are the same as those of a normal inspiration of the same depth.

These observations have clinical significance. During the administration of controlled respiration, the anesthetist need have no more concern for the effects of positive pressure on the pulmonary circulation than he would if the patient were breathing normally. His only concern, therefore, is for the effects of the positive pressure on the systemic circulation.

If the direct effects of positive-pressure breathing and normal breathing on the lungs are the same, we must look elsewhere for an explanation for the reported benefits of positive-pressure breathing in treating pulmonary edema, emphysema, and disturbances in the alveolar ventilation-perfusion ratio. The benefit of positive-pressure breathing on pulmonary edema has already been explained on the basis of its effects on the systemic circulation. Improvement in the ventilation-perfusion ratio with pressure breathing has been attributed to the opening of obstructed alveoli.[6] By reasoning from the experimental data above, it can be predicted that the same results could be obtained by the positive atmospheric pressure that inflates the lungs during normal breathing. This can be explained as follows:

Pressure breathing has the additional effect of causing the subject to breathe at a position of increased thoracic volume (increased functional

residual capacity). Increased thoracic volume increases bronchial diameter and opens up obstructed alveoli. Experiments reported elsewhere[7] have demonstrated that the same dilation of the bronchi can be achieved without positive pressure simply by voluntarily breathing in a position of increased lung volume.

Controlled Respiration In Anesthesia

Since it has been demonstrated by many investigators that positive-pressure breathing is well tolerated by the normal individual, the anesthetist may employ controlled respiration in any normal individual in a reasonable manner without fear of harmful consequences. A patient whose circulation is depressed by barbiturates or deep anesthesia of any kind, or whose vasomotor tone is altered as the result of spinal anesthesia or ganglionic blocking agents, will have an adverse circulatory reaction to pressure breathing. This will be characterized by a sharp reduction in blood pressure and cardiac output. In the operating room, under ideal circumstances, such a reaction is not necessarily a deterrent to the use of positive-pressure breathing. The anesthetist has readily available the means of increasing blood volume, restoring vasomotor tone, or lightening the depth of anesthesia. Whenever controlled respiration is necessary to maintain pulmonary ventilation, or for any other reason, the anesthetist may administer it and take the measures necessary to maintain an adequate cardiac output. It has been demonstrated that the degree of circulatory depression caused by pressure breathing is directly related to the mean airway pressure.[5] Therefore the use of alternating positive and negative airway pressure will produce a lower mean mask pressure and will affect blood pressure and cardiac output less than positive pressure alone, even in patients in very poor condition. In the presence of an adverse reaction to controlled respiration, the anesthetist has two choices: (1) to support vigorously the patient's systemic circulation; or (2) to use alternating positive-negative pressure respiration with a low mean airway pressure.

The choice of respirators for use by emergency crews is quite another matter. Since lay individuals have neither the means nor the knowledge to support the circulation of the apneic individual, they should be supplied with a respirator of low mean mask pressure. This is most effectively accomplished by the use of an alternating positive-negative type machine.

Summary

The effects of pressure breathing on the systemic and pulmonary circulations are reviewed. The direct effects of pressure breathing on the pulmonary circulation are demonstrated by experiment to be the same as those of normal respiration, for equal changes of lung volume. The effects on the systemic circulation may be quite different for different types of respiration, and these effects may secondarily influence the pulmonary circulation. Controlled respiration applied to normal individuals by any reasonable

method will be well tolerated. Under conditions of circulatory stress, controlled respiration may produce a profound depression of blood pressure and cardiac output. The anesthetist may combat this depression by vigorously supporting the patient's systemic circulation, or by the use of pressure breathing with a low mean mask pressure.

Correction

In a previous publication on this subject[5] the senior author stated that the maximal differential pressure across the lungs developed during performance of a vital capacity test is 45 mm. Hg. This figure should be 25 mm. Hg. Although the intact thorax may tolerate a total pressure of 45 mm. Hg, the differential pressure across the lungs will be considerably less.

References

1. Barach, A. L., W. O. Fenn, E. B. Ferris & C. F. Schmidt. 1947. The physiology of pressure breathing; a brief review of its present status. J. Aviation Med. **18:** 73.
2. Beecher, H. K., H. S. Bennett & D. L. Bassett. 1943. The circulatory effects of increased pressure in the airway. Anesthesiology. **4:** 612.
3. Carr, D. T. & H. E. Essex. 1946. Certain effects of positive pressure respiration on the circulatory and respiratory systems. Am. Heart J. **31:** 53.
4. Maloney, J. V., Jr., J. E. Affeldt, S. J. Sarnoff & J. L. Whittenberger. 1951. Electrophrenic respiration. IX. Comparison of effects of positive pressure breathing and electrophrenic respiration on the circulation during hemorrhagic shock and barbiturate poisoning. Surg. Gynecol. Obstet. **92:** 672.
5. Maloney, J. V., Jr., J. O. Elam, S. W. Handford, G. A. Balla, D. W. Eastwood, E. S. Brown & R. H. Ten Pas. 1955. Importance of negative pressure phase in mechanical respirators. J. Am. Med. Assoc. **152:** 212.
6. Motley, H. L., L. P. Lang & B. Gordon. 1950. Effect of intermittent positive pressure breathing on respiratory gas exchange. J. Aviation Med. **21:** 14.
7. Maloney, J. V., Jr., A. B. Otis, W. O. Fenn & J. L. Whittenberger. 1950. The effect of positive pressure breathing on air flow resistance of the tracheobronchial tree. J. Clin. Invest. **29:** 832.

THE METHODOLOGY OF CONTROLLED RESPIRATION

By David M. Little, Jr.

Department of Anesthesiology, Hartford Hospital, Hartford, Conn.

Almost half a century ago—a very long time, indeed, in terms of anesthetic techniques—two farsighted Germans, Brat and Schmieden, in a classical review on anesthesia for chest surgery, "came to the conclusion that artificial respiration by inflating the lungs when the chest was open would be more efficient if the patient's own respiration could be abolished. They suggested that this abolition could be accomplished either by the injection of curare which would paralyze the respiratory musculature . . . or by the production of deep anesthesia."[1] In retrospect, their clairvoyance seems incredible, for this is an adequate description of two of the pharmacological means presently employed for the production of controlled respiration.

A year later, in 1909, the American surgeons Janeway and Green described Green's laboratory technique,[2] which employed a mechanical pump to inflate and deflate the lungs rhythmically: "In working with the intralaryngeal cannula it was noticed that the alternating increase and decrease in intratracheal pressure produced an artificial apnoea which largely eliminated the movements of the diaphragm. The advantages of such an elimination of movement during operation were . . . apparent."[3] Here, again, the anticipation was remarkable; this statement is an apt description of one of the mechanical means for the production of controlled respiration in use today.

Thirty years were to elapse, however, between these pioneer descriptions of the methodology of controlled respiration and the introduction of these methods into clinical anesthetic practice. In 1934, Guedel and Treweek[4] resurrected the concept in the technique that they called "ether apnoea"; 2 years later, in 1936, Waters[5] described the method in relation to cyclopropane anesthesia and gave the technique its present name, controlled respiration.

Definitions

Controlled respiration may be defined as a method of inducing artificial respiration during anesthesia in which the spontaneous respiratory activity is abolished, and the rate, rhythm, depth, and phasing of respiratory movements are then supplied for the patient by the anesthesiologist. Controlled respiration is quite distinct from assisted respiration. The latter is an intermittent augmentation of the patient's own inspiratory effort: the rate, rhythm, and phasing of respiration remain under the control of the patient's respiratory mechanisms, and the anesthesiologist merely increases the degree of inspiratory volume without attempting to take over the control of respiration. Controlled respiration is accomplished by a disintegration of the normal physiological and biochemical aspects of respiratory control, and the subsequent substitution of artificial methods of ventilation for the

patient's own respiratory efforts. Such a disintegration of normal respiratory control may be effected either by pharmacological or by mechanical means; but, because of the very nature of the factors that exert control over respiration, it is accomplished most reasonably by the two acting in concert.

The Control of Respiratory Movements

The methodology of controlled respiration is derived from those factors that regulate the breathing process in normal, unanesthetized man. Of prime importance among these are the activities of the respiratory center. This center is really an integrated complex of 3 groups of cells in the reticular formation of the pons and the medulla oblongata, consisting of a dorsal expiratory center and a ventral inspiratory center in the medulla, and a pontine pneumotaxic center.[6, 7] Inspiration is the result of a discharge from the medullary inspiratory center to the neurons innervating the inspiratory muscles. As the inflation process proceeds, pulmonary stretch receptors scattered in the walls of the respiratory bronchioles, of the alveolar ducts, and of the air sacs are stimulated, and mechanical distension of the lungs produces the discharge of a repetitive train of afferent impulses.[8] When a certain degree of inflation has been reached, reflex inhibition of the inspiratory center results from these afferent vagal impulses, and inspiration ceases. This well-known mechanism of autoregulation of the rhythm of breathing, postulated by Hering and Breuer in 1868, is of fundamental importance to the anesthesiologist employing controlled respiration. The existence of a Hering-Breuer reflex subserving deflation also has been shown experimentally; forced deflation of the lungs stimulates "deflation" receptors and initiates inspiration.[8, 9]

A large number of other neural mechanisms influence the activity of the respiratory center, but they are of secondary importance in the production of controlled respiration. The chemoreceptor reflexes from the carotid and aortic bodies, however, deserve special mention. They do not respond to stretch stimuli as do the pressoreceptors lying adjacent to them in these locations, but react rather to a decrease in oxygen tension and, to a lesser extent, to a rise in carbon dioxide tension. Afferent impulses from the aortic and carotid bodies stimulate the respiratory center continuously, but an almost linear increase in the frequency of these nerve impulses occurs as the oxygen saturation of the arterial blood falls below 95 per cent. An increase in arterial carbon dioxide tension is also stimulatory, but the response is of much smaller magnitude.

The respiratory drive of anoxia is mediated chiefly through these chemoreceptor mechanisms, for the direct effect of anoxia—particularly severe anoxia—upon the respiratory center is one of depression. The center is, however, stimulated by, and exquisitely sensitive to, minute changes in the partial pressure of carbon dioxide and in the hydrogen-ion concentration of the arterial blood perfusing the medulla. The mechanism of action of carbon dioxide upon the respiratory centers appears to be a direct cen-

tral effect,[10] and stimulation of respiration by carbon dioxide is not decreased significantly by denervation of the carotid and aortic bodies. The precise mode of action of carbon dioxide upon the respiratory center has been the subject of considerable discussion. However, from the practical point of view of the production of controlled respiration during operation, it suffices merely to recognize the fact that "carbon dioxide is the stimulant *par excellence* of respiration."[11]

The syndrome of general anesthesia produces widespread protoplasmic poisoning that modifies in a number of important ways the various factors exerting control over respiratory activity.[12] "The balance between chemical and nervous factors in respiratory control is disturbed by narcotic drugs, but the degree and even the type of the disturbance vary according to the drug, perhaps also according to the individual. The single common result of all narcotics is a *decrease* in the sensitivity of the respiratory center to increased carbon dioxide in the blood."[13] This is true of all of the general anesthetic agents in common use today, with the single exception of nitrous oxide when it is administered without the production of hypoxia; but this is not to say that all of these drugs, when administered in moderate dosage, will decrease the respiratory minute volume, for pulmonary ventilation may be maintained at or above the normal level because of reflexes elicited by the local irritant properties of such agents as ethyl or vinyl ether, or because of a rise in the partial pressure of carbon dioxide in the arterial blood adequate to match the elevated threshold of the respiratory center.[14]

The general anesthetic agents also may modify, to a very considerable degree, the chemoreflexes subserved by the carotid and aortic bodies.[15] Ether, cyclopropane, and chloroform depress these chemoreflexes;[13, 16, 17] nitrous oxide, when administered without the production of hypoxia, has no influence upon them;[18] and morphine, Pentothal, Evipal, Nembutal, and Avertin all accentuate them.[13, 16, 19–21]

The various anesthetic drugs also affect the activity of the Hering-Breuer reflex, as well as the excitability of the pulmonary receptors that are responsible for the reflex itself. It is worth noting that the effects are by no means identical, and that, in fact, the pulmonary inflation and deflation receptors, and the Hering-Breuer reflex, may be affected quite differently by a given anesthetic agent. It has been shown that all of the volatile and gaseous anesthetic agents increase the frequency of respiratory afferent nerve impulses in the vagus nerve by 30 to 140 per cent as a result of the increased excitability of the pulmonary inflation receptors; all of the volatile agents, following the initial stimulation, then produce a depression of excitability that is proportional to the concentration of the agent. Nitrous oxide and cyclopropane do not cause a similar concurrent depression.[22] On the other hand, the Hering-Breuer reflex itself is exaggerated during anesthesia produced by the barbituric acid derivatives, even though the latter depress the activity of the receptors.[22] Chloroform, cyclopropane, and ether all depress the Hering-Breuer reflex.[23]

From the point of view of the methodology of controlled respiration,

there are, therefore, several factors concerned with the normal regulation of pulmonary ventilation that may be altered for the purpose of abolishing the patient's own spontaneous respirations.

First, the respiratory center itself may be depressed by the action of narcotic and anesthetic agents to the point at which it is not responsive to normal concentrations of carbon dioxide tension in the arterial blood. In instances in which the amount of narcotic or anesthetic agent approaches, in effect, an overdosage, the depression of the respiratory center progresses, of course, to apnea; but the depressive action of these drugs may be utilized also in doses considerably less than the apneic dose to facilitate the control of respiration, in conjunction with other maneuvers, by rendering the center simply less responsive to the usual respiratory drives.

Second, following the depression of the medullary respiratory centers with narcotic or anesthetic drugs, the anoxic drive from the chemoreflexes may be abolished by the use of high concentrations of oxygen. This is the "oxygen apnea" described by Marshall and Rosenfeld,[21] and it is a phenomenon that may occur following heavy premedication with an opiate, the use of an intravenous barbiturate for the induction of anesthesia, and the administration of a potent, rapid-acting respiratory depressant such as cyclopropane. Depressed respirations lead to hypoxemia, which becomes the chief stimulus to respiratory activity, and a single breath of oxygen may then suffice to eliminate chemoreceptor control and produce apnea. Burstein has demonstrated the role that anticholinergic drugs, such as atropine and scopolamine, may play in the production of such an apnea, presumably due to the depressant effect of these parasympathetic-blocking substances on the carotid body mechanism.[24]

Third, the carbon dioxide tension of the arterial blood, normally a significant stimulus to the respiratory center, may be lowered to such a degree as to become inadequate as a stimulus. In a given patient with a constant production of carbon dioxide, and in the absence of circulatory shunts, the arterial tension of carbon dioxide is a direct function of the alveolar ventilation. Changes in alveolar ventilation will cause changes in the alveolar and arterial tensions of carbon dioxide that are inversely proportional to the magnitude of the alveolar ventilation. Under circumstances in which no rebreathing of carbon dioxide occurs and in which alveolar membrane permeability is preserved and capillary blood is delivered to all the various segments of the lung in sufficient amount, alveolar hyperventilation will lower the arterial carbon dioxide tension below the threshold of the center for that gas.

Fourth, stimulation of pulmonary inflation receptors within the lungs will activate the Hering-Breuer reflex, increasing the stream of vagal impulses, which inhibit further inspiratory activity. Indeed, the view has been expressed that activation of the regulatory Hering-Breuer reflex, or hyperinflation as contrasted with hyperventilation, is more important in the production of controlled respiration than the diminution of response to carbon dioxide stimulation. Burstein[25] has shown that, when rebreathing was per-

mitted prior to the institution of intermittent positive pressure synchronous with inspiration, the carbon dioxide tension of the arterial blood was raised from a preanesthetic level of 47.4 volumes per cent to 54.7 volumes per cent. His thesis has been that overinflation and the Hering-Breuer reflex were more important in producing apnea than was the reduced tension of carbon dioxide. On the other hand, it has been pointed out[15] that the inhibition of respiration by the Hering-Breuer reflex does not persist longer than the inflation of the lung, since afferent inhibitory impulses appear in the vagus nerve only during inflation. The concept of respiratory center "fatigue" has been put forward to account for these divergent facts; it has been postulated[26] that there is an accumulation of the Hering-Breuer inhibitory reflex that produces prolonged inhibition of the respiratory center because of frequent and exaggerated pulmonary distension. Actually, it is extremely difficult to separate the effects of hyperventilation and hyperinflation in controlled respiration, for the two necessarily go together during the maneuver.

Finally, spontaneous respiratory movements may be abolished by paralysis of the muscles of respiration. This is an attack upon the periphery of the respiratory mechanism that is remarkable because the respiratory center itself, the chemoreceptors, the level of the carbon dioxide tension in the arterial blood, and the status of the Hering-Breuer reflex are involved only secondarily: paralysis of the muscles of respiration is quite sufficient to produce total apnea.

Pharmacological Methods

The pharmacological methods for producing controlled respiration therefore include: those based upon depression of the respiratory center by the use of narcotic and anesthetic drugs; those based upon obtundation of chemoreceptor activity; and those based upon paralysis of the peripheral musculature. From a theoretical point of view, it is logical to consider these pharmacological methods separately from the mechanical methods; in fact, of course, it is impossible to ignore the interdependent relationship between the two. No matter what pharmacological means may be employed to induce apnea and gain control of respiration, resort must be had to some mechanical means—be it the human hand or a machine—for the maintenance of ventilation during controlled respiration.

The purest of the pharmacological methods is perhaps the "passive" form of controlled respiration employed during cyclopropane anesthesia by Guedel[27] many years ago. Cyclopropane is such a potent respiratory depressant that it is capable of elevating the threshold of the respiratory center far above the level of activation of the normal stimuli. The inhalation of high concentrations of the gas will cause apnea, and artificial respiration during this period of apnea produces controlled respiration. This technique is, in reality, a depression of the respiratory center by what amounts to stage IV anesthesia, and thus may be employed with any total anesthetic agent.

A second pharmacological method for producing controlled respiration is the technique of "oxygen apnea" to which I have already referred in the consideration of the chemoreceptors. This technique requires depression of the respiratory center by the administration of opiates or barbiturates, followed by further depression with an anesthetic agent. Respiratory activity is then depressed and is maintained only by the stimulation of the carotid-body mechanism by hypoxemia. When this hypoxemic stimulus is removed by the presentation of a high concentration of oxygen to the patient, apnea results, and ventilation is then carried out by the anesthesiologist. The method has been utilized in the past, but the asphyxial stimulation of respiration is to be condemned, and the technique is now mainly of academic interest.

The third pharmacological method, the one that enjoys the greatest popularity, is the administration of muscle-relaxant drugs to produce peripheral respiratory paralysis. The British have emphasized the difference between what was ominously called "respiratory arrest," the danger signal of yesterday, and "apnea," the desirable phenomenon today, which has resulted from this use of myoneural blockade for the purpose of instituting controlled respiration.[28] In the muscle-relaxant technique, the patient is anesthetized lightly and then rendered apneic by the use of curare, succinylcholine, or some other muscle-relaxant preparation; artificial ventilation is then instituted.[29]

Mechanical Methods

The mechanical methods for producing controlled respiration are based upon hyperventilation and hyperinflation and may be performed by the manual application of intermittent positive pressure to the breathing bag of the anesthesia machine, by a positive-pressure respirator, or by a positive-negative pressure respirator. There are only rare instances when purely mechanical means are employed for the production of controlled respiration. One example might be the assistance of inspiration, during the inhalation of oxygen alone, at an increasingly rapid rate until apnea is produced: controlled respiration would then be instituted. This technique can be utilized for endotracheal intubation in infants, and in elderly, cachectic patients whose respiratory musculature can be overcome by the use of positive pressure. For the most part, however, just as the pharmacological methods depend upon the use of mechanical means for ventilation, so, too, do the mechanical methods depend upon pharmacological means for the production of apnea and the institution of control.

There are certain requisites of ventilation during controlled respiration by mechanical means that the anesthesiologist must attempt to fulfill, whether he employs his hand or a machine for the purpose. The peak positive pressure applied should be kept below 30 cm. of water. Pressures in excess of this that might injure the lungs are unlikely during manual ventilation with a thin rubber breathing bag, but a safety valve of some sort should be included in mechanical devices employed to produce intermittent positive

pressure. A peak pressure of 20 or 25 cm. of water is required to inflate the lungs of an apneic patient when the chest wall is intact. The necessary pressure is somewhat less, 10 to 15 cm., when the chest has been opened and only the elasticity of the lungs must be overcome; however, the presence of retractors during intrathoracic operations may impede adequate ventilation and again necessitate pressure in the range of 20 to 25 cm. of water.[30] If the minute volume ventilation is to be sufficient to ensure oxygenation and the effective removal of carbon dioxide, the tidal volume must be measured directly and maintained at a level comparable to that of the patient's resting tidal exchange.[31] The rate of ventilation, therefore, must be correlated with the tidal volume in order to ensure an adequate minute volume; it must not, however, be so rapid as to cause a reduction of cardiac output.[32-34] The phasing of the respiratory cycle is of great importance, both from the point of view of gaseous exchange within the lungs and because of possible deleterious effects upon the circulation: it has been established that inspiration should occupy only one third or one quarter of the entire cycle, and indeed, a large proportion of the tidal air may be obtainable by an inspiratory phase lasting only 0.6 sec.,[35] if the onset of pressure is sufficiently rapid to produce a "square" type volume-time curve.[36]

The performance of controlled respiration by the method of applying intermittent positive pressure to the breathing bag of the anesthesia machine with the hand, therefore, should consist of the rather sudden application of pressure for a period of a second or so, with a complete release of the hand after maintaining pressure just long enough to achieve the resting tidal volume; expiration, which is entirely passive, is accomplished by leaving one's hand off the bag for a period of time that is at least twice as long as that taken for the inspiratory phase, and is followed by a pause. The next respiratory cycle is then begun and conducted in similar fashion, the exact duration of each cycle being dependent upon the ventilatory rate necessary to produce an adequate minute volume for the individual patient's tidal volume. Definite advantages can accrue from such use of the hand, rather than of a machine, in the performance of these techniques. The depth of anesthesia, or the degree of myoneural blockade, can be assessed to some extent by the perception of resistance to inflation.[37] In similar fashion, the onset of such conditions as bronchospasm, respiratory obstruction, or the accumulation of secretions, can be recognized by the "educated hand."[38] Respiratory movement can be stopped altogether, and instantaneously, for short periods of time during any particularly difficult surgical manipulation; an advantage, it might be added, that is now also built into the more modern respirators. The technique of producing intermittent positive pressure by squeezing the breathing bag requires no extra apparatus, employs no special source of power, and is readily available at all times. It is, however, extremely difficult to perform properly; and it requires education of the hand in conjunction with the use of a pressure manometer, a ventilometer, and a stopwatch to time the phasing of the ventilatory cycle if the results are to approach those achieved by mechanical respirators.

Positive-pressure respirators may be classified into two categories as "pump-type" or "pressure-sensitive" machines.[30] The basic mechanism of the pump-type respirator is that a preset, or fixed, volume of gas is delivered into the lungs at each stroke of the pump. The fundamental disadvantage of these respirators is that the machine, as are all machines, is inexorable, and is bound to deliver the preset volume regardless of the pressure developed within the lungs. The incorporation of a safety valve has proved to be only a partial solution to this problem, for if the pressure to which the valve is set is exceeded before the machine has completed its cycle, the lungs will be held distended until the pump has reached the end of its stroke. The early respirators of Pinson and Bryce[39] and of Mörch,[40] the James Respirator,[41] the Beaver Respirator,[42] and the Radcliffe Respiration Pumps,[44] are all examples of the pump type of respirator.

The pressure-sensitive respirators, on the other hand, respond to preset pressures reached within the chest, and cycle when that pressure is reached; the intrathoracic pressure falls quickly toward the atmospheric. Cycling is dependent upon a manometric device, such as a diaphragm, a water manometer, or a bellows, to actuate the valves. The great disadvantage of these respirators is that activation of the valves will occur when the preset pressure has been reached, irrespective of the volume of gas that has been delivered into the lungs. Obviously, respiratory obstruction, bronchoconstriction, the pressure of retractors, or manipulation of the lung by the surgeon, may serve to trigger such a cycling mechanism. Crafoord's original spiropulsator,[45] the Blease Pulmoflator,[46] and the Emerson Assistor,[47] are all examples of pressure-sensitive devices for the rhythmic inflation of the lungs. The more recent machines of this type are actuated by electrically operated valves.[48–51] and introduce yet another problem into the operating room in view of the explosive hazard presented by many anesthetic agents.

Physiologists have frequently reiterated that deleterious effects upon both the circulatory system and the respiratory exchange of gases may result from the use of positive pressure, whether accomplished by manual means or by a mechanical respirator. They have advocated the use of positive-negative pressure machines, which would provide not only positive pressure during inspiration but also negative pressure during exhalation. These so-called "suck-and-blow" respirators are becoming among the most commonly employed automatic devices for ventilation during controlled respiration. They include such newly developed machines as the Jefferson Ventilator,[43] the Fazakerly Respirator,[52] and the Stephenson Ventilator, as well as the modification of earlier models of Pinson's Pulmonary Pump,[53] the Blease Pulmoflator,[54] and the Radcliffe Pulmonary Pumps[55] by the addition of a mechanism for negative pressure. Controlled respiration can be induced with amazing facility by the use of these respirators, and it is possible that the deflationary arm of the Hering-Breuer reflex is called into play in such instances.

There are definite advantages in the employment of automatic devices for

rhythmic inflation of the lungs during controlled respiration. The volume, rate, rhythm, and phasing of respiration are reproducible, from one respiratory cycle to the next, far more consistently by a machine than by the most educated hand,[38] since even vigorous manual compression of the breathing bag may produce relative ventilatory inefficiency and permit the development of respiratory acidosis.[43] This is particularly true during prolonged operative interventions, when the strongest hand may succumb to the monotony of rhythmically squeezing a bag for long periods of time.[39] Of more importance, these machines free the anesthesiologist's hands, and permit him greater mobility to concentrate on the care of the patient. It has been shown that apneic pauses of as long as 80 sec. may occur during manually controlled respiration while an intravenous infusion is being adjusted, a blood transfusion is initiated, or the trachea is being subjected to suction, and that such pauses produce sharp rises in the arterial and alveolar carbon dioxide tensions.[56]

Automatic respirators are not without their disadvantages, however. They are capable of creating a false sense of security, the comfortably regular click of the machine suggesting that all is well, when, in fact, quite the reverse may be true. Furthermore, these respirators are subject to failure at any time without warning. Such failures necessitate an immediate return to manual methods of ventilation and make mandatory the incorporation of a mechanism for this purpose into every respirator designed for operating-room use. The greatest disadvantage of all mechanical methods of ventilation during controlled respiration, however, is that even if the minute volume ventilation for which they are preset is delivered to the lungs, it cannot be assumed that the necessary alveolar ventilation will be accomplished, since variations in resistance and compliance throughout the lung may lead to unequal ventilation.

Combined Methods

The pharmacological methods and the mechanical methods have been described as separate entities; but it must be emphasized that this is a convenience of semantics, for it is only when they are employed together in the combined methods of controlled respiration that they are of real importance. The combined methods in most common clinical use are two in number: one based primarily on depression of the respiratory center, in conjunction with the use of hyperventilation and hyperinflation; and the other based primarily on paralysis of the peripheral musculature, again in conjunction with the use of hyperinflation and hyperventilation. Because anesthesiologists are individualists, there is considerable overlap between the two techniques.

The first of these two techniques employs ether, cyclopropane, or a similar potent agent for the depression of the respiratory center during anesthesia, but differs from the technique of respiratory-center depression described under the pharmacological methods in that the depressive action of the anesthetic agent is utilized in doses considerably less than the apneic

and in combination with hyperventilation to reduce the concentration of carbon dioxide in the blood.[57] Anesthesia is established to a moderate depth (plane II) with ether or cyclopropane, employing a closed system with absorption of carbon dioxide, and the volume of inspiration then is augmented by mechanical means. As such augmentation continues, the tension of carbon dioxide in the blood is reduced by the hyperventilation below the level necessary to stimulate the depressed respiratory center; spontaneous respirations cease; and controlled respiration is established.[58] If, at the same time that augmentation of respirations is begun, the concentration of the anesthetic agent also is increased, controlled respiration will be established more rapidly;[27] but, of course, the danger of overdosage will be increased to a similar extent. The classic concept of this combined technique always has stressed the importance of hyperventilation for the reduction of carbon dioxide tension below the level to which the depressed respiratory center would respond; but the role of hyperinflation in the production of controlled respiration by this technique cannot be doubted in certain instances in which there are few respirations prior to the onset of apnea.

The second of these combined techniques resembles that described under the pharmacological methods for the production of apnea by the use of muscle-relaxant drugs during anesthesia. It differs, however, in that the entire burden of the apneic state is not borne by the muscle-relaxant drug alone, but in conjunction with the effects of hyperinflation, and perhaps also of hyperventilation, upon the respiratory mechanism.[29, 50] Anesthesia is induced by the intravenous administration of an ultrashort-acting barbiturate such as Pentothal, and it is maintained by the use of nitrous oxide-oxygen in 50:50 concentration, with the occasional intravenous supplementation of a more potent specific analgesic such as Demerol. Curare, succinylcholine, or a similar muscle-relaxant preparation then is administered to produce muscular relaxation; at the same time artificial ventilation by one of the mechanical means is begun.[59, 60] If complete muscular paralysis results from the injection of the muscle-relaxant drug, controlled respiration is established immediately; if the dosage of muscle-relaxant preparation has been subapneic, hyperinflation, and to some extent perhaps hyperventilation, soon produces apnea and the onset of controlled respiration. Even in the event of immediate apnea, however, hyperinflation and hyperventilation are not without their effects upon the controlled state, inasmuch as they permit the use of much smaller doses of relaxant drug during the procedure than would be possible in the absence of controlled respiration.[61] During this type of anesthesia the patient is very close to consciousness, and the technique therefore differs considerably from that depending upon the profound depression of deep general anesthesia following the use of ether, cyclopropane, or Pentothal, for the purpose of inducing respiratory arrest.

The Dangers Inherent in the Methods of Controlled Respiration

The methodology of controlled respiration can be summarized best by a critique of the dangers inherent in the methods themselves. The fallibility of mechanical ventilation, particularly by the manual method, resides in the fact that the "educated" hand is not as learned as one might wish it to be for purposes of adequate respiratory exchange. The pressure employed, the tidal volume actually moved, and the rate of ventilation are all of importance; the phasing of the inspiratory and expiratory segments of the ventilatory cycle is also of major significance. It is asking a great deal of the human hand to provide, say, a tidal air of 460 cc., at a pressure of 10 cm. of water during an inspiration lasting 1 sec. and at a rate of 15 cycles per min.[31] Less stringent requirements, however, lead inevitably to inadequate alveolar gaseous exchange and the probability of acidosis. This danger has become fact on a sufficient number of occasions to precipitate a preference for automatic devices for rhythmic inflation of the lungs.

This preference has led to the production of a number of ventilators that will inflate the lungs at a proper pressure, rate, and volume and, at the same time, will phase the ventilatory cycle correctly. These machines, however, do not mitigate the unpleasant results of positive pressure upon the circulatory system. The adverse effects of continuous positive pressure upon the cardiac output, venous pressure, and venous return to the heart are too well known to require further elaboration.[62, 63] However, the consequences of intermittent positive pressure are also of importance in this regard for, even when positive pressure is applied to the airway on an intermittent basis, the mean intratracheal pressure is raised above atmospheric pressure, and there is some decrease in both venous return and cardiac output.[64] When the circulatory status of the patient is good and the rise in mean intratracheal pressure is slight, the problem may not be of clinical significance; but it becomes significant and of great urgency when the patient's circulatory status is deteriorating.[65]

The positive-negative pressure respirator, by providing a mean intratracheal pressure that is not elevated, has solved these circulatory difficulties in some measure and has focused attention upon a final danger that is not unique as regards the use of these particular machines (although perhaps it is emphasized by them) but is prevalent in all the methods of controlled respiration. It is the danger that, although the control of respiration is established, control of the over-all anesthetic state may be lost. The anesthesiologist's best sign of the anesthetic state has always been the behavior of the respiratory system; the other signs—color, blood pressure, pulse, pupillary size, eyeball activity, presence or absence of sweating, capillary refilling time, reflex responses, and muscle tone—were correlated with that major sign in order to evaluate the depth of, and need for, anesthesia. The dangers of overdosage from either the fully potent agents or from a muscle relaxant, or of underdosage—and more than one patient has been terrifyingly awake during the ordeal of operation when the muscle-relaxant

technique has been employed—are very real during controlled respiration. Every anesthesiologist has had to develop his own particular signs or intuition to lead him through the maze, for today the mechanical methods of controlled respiration are in the ascendancy over the pharmacological methods. Perhaps the future solution will lie in the use of electroencephalographic control of the anesthetic state, in conjunction with positive-negative pressure ventilation, for the production of controlled respiration.

References

1. Brat, H. & V. Schmieden. 1908. Munch. Med. Wchnschr. **55:** 2421. *Quoted in* The Principles of Thoracic Anaesthesia Past and Present. 1953. W. W. Mushin & L. Rendell-Baker, Eds. Charles C. Thomas. Springfield, Ill.
2. Green, N. W. 1906. Surg. Gynecol. Obstet. **2:** 512.
3. Janeway, H. H. & N. W. Green. 1909. J. Am. Med. Assoc. **53:** 1975.
4. Guedel, A. & D. N. Treweek. 1934. Current Researches Anesthesia & Analgesia. **13:** 263.
5. Waters, R. M. 1936. Proc. Roy. Soc. Med. **30:** 11.
6. Lumsden, T. 1923. J. Physiol. **57:** 153.
7. Pitts, R. F., H. W. Magoun & S. W. Ranson. 1939. Am. J. Physiol. **126:** 673, 689.
8. Adrian, E. D. 1933. J. Physiol. **79:** 332.
9. Partridge, R. 1933. J. Cellular Comp. Physiol. **2:** 367.
10. von Euler, C. & U. Soderberg. 1952. J. Physiol. **118:** 555.
11. Wright, S. 1947. Applied Physiology. Oxford Univ. Press. London, England.
12. Krogh, A. 1941. The Comparative Physiology of Respiratory Mechanisms. Univ. Pa. Press. Philadelphia, Pa.
13. Schmidt, C. F. 1944. Anesthesiology. **5:** 77.
14. Schmidt, C. F. 1954. *In* Pharmacology in Medicine. V. A. Drill, Ed. McGraw-Hill. New York, N. Y.
15a. Watrous, W. G., F. E. Davis & B. M. Anderson. 1950. Anesthesiology. **11:** 538, 661.
15b. Watrous, W. G., F. E. Davis & B. M. Anderson. 1951. Anesthesiology. **12:** 33.
16. Dripps, R. D. & P. R. Dumke. 1943. J. Pharmacol. Exptl. Therap. **77:** 290.
17. Burstein, C. L. 1940. N. Y. State J. Med. **40:** 1767.
18. Clement, F. W. 1951. Nitrous Oxide-Oxygen Anesthesia. Lea & Febiger. Philadelphia, Pa.
19. Moyer, C. A. 1941. J. Thoracic Surg. **11:** 131.
20. Moyer, C. A. & H. K. Beecher. 1942. J. Clin. Invest. **21:** 429.
21. Marshall, E. K. & M. Rosenfield. 1936. J. Pharmacol. Exptl. Therap. **57:** 437.
22. Whitteridge, D. & F. Bulbring. 1944. J. Pharmacol. Exptl. Therap. **81:** 340.
23. Schmidt, C. F. & W. B. Harer. 1923. J. Exptl. Med. **37:** 69.
24. Burstein, C. L. 1941. Anesthesiology. **2:** 530.
25. Burstein, C. L. & E. A. Rovenstine. 1939. Am. J. Surg. **43:** 26.
26. Cordier, D. & C. Heymans. 1935. Ann. physiol. physicochim. biol. **11:** 630.
27. Guedel, A. E. 1940. Anesthesiology. **1:** 13.
28. Leading Article. 1953. Brit. Med. J. **1:** 875.
29. Harroun, P., F. E. Beckert & H. R. Hathaway. 1946. Anesthesiology. **7:** 24.
30. Mushin, W. W. & L. Rendell-Baker. 1954. Brit. J. Anaesthesia. **26:** 131.
31. Spalding, J. M. K. 1955. Lancet. **1:** 1099.
32. Cournand, A., H. L. Motley, L. Werko & D. W. Richards, Jr. 1948. Am. J. Physiol. **152:** 162.
33. Motley, H. L., A. Cournand, L. Werko, D. T. Dresdale, A. Himmelstein & D. W. Richards, Jr. 1948. J. Am. Med. Assoc. **137:** 370.
34. Hubay, C. A., R. C. Waltz, G. A. Brecker, J. Praglin & R. A. Hingson. 1954. Anesthesiology. **15:** 445.
35. Spalding, J. M. K. & S. A. Young. 1955. Lancet. **2:** 227.
36. Maloney, J. V., Jr. & S. W. Handford. 1954. J. Appl. Physiol. **6:** 453.
37. Rollason, W. N. 1956. Can. Anaesthesia Soc. J. **3:** 68.

38. Cullen, S. C., J. H. Comroe, Jr., E. B. Brown, Jr., H. K. Beecher & J. V. Maloney, Jr. 1954. Anesthesiology. **15**: 416.
39. Pinson, K. B. & A. G. Bryce. 1944. Brit. J. Anaesthesia. **19**: 53.
40. Mörch, E. T. 1947. Proc. Roy. Soc. Med. **40**: 603.
41. James, N. R. 1950. Med. J. Australia. **1**: 325.
42. Beaver, R. A. 1953. Lancet. **1**: 977.
43. Albritten, F. F., Jr., G. J. Haupt & J. H. Amadeo. 1954. Ann. Surg. **140**: 569.
44. Russell, W. R. & E. Schuster. 1953. Lancet. **2**: 707.
45. Crafoord, C. 1950. J. Thoracic Surg. **9**: 237.
46. Musgrove, A. H. 1952. Anaesthesia. **7**: 77.
47. Maloney, J. V., Jr., W. S. Derrick & J. L. Whittenberger. 1952. Anesthesiology. **13**: 23.
48. Bang, C. 1953. Lancet. **1**: 723.
49. Macrae, J., G. D. W. McKendrick, J. M. Claremont, E. M. Sefton & R. V. Walley. 1953. Lancet. **2**: 971.
50. Mörch, E. T. 1948. Anaesthesia. **3**: 4.
51. Pask, E. A. 1953. Lancet. **1**: 141.
52. Esplen, J. R. 1956. Brit. J. Anaesthesia. **28**: 176.
53. Pinson, K. B. 1949. Anaesthesia. **4**: 79.
54. Horton, J. A. G., J. S. Inkster & E. A. Pask. 1956. Brit. J. Anaesthesia. **28**: 169.
55. Russell, W. R., E. Schuster, A. C. Smith & J. M. K. Spalding. 1956. Lancet. **1**: 539.
56. Stead, W. W., F. E. Martin & N. K. Jensen. 1953. J. Thoracic Surg. **25**: 435.
57. Nosworthy, M. D. 1951. Proc. Roy. Soc. Med. **34**: 479.
58. Gillespie, N. A. 1948. Endotracheal Anesthesia. Univ. Wisconsin Press, Madison, Wis.
59. Gray, T. C. & G. J. Rees. 1952. Brit. Med. J. **2**: 891.
60. Rumble, L., Jr., A. R. Gholson & M. P. Peters. 1955. Current Researches Anesthesia & Analgesia. **34**: 261.
61. Dundee, J. W. 1952. Brit. Med. J. **2**: 893.
62. Beecher, H. K., H. S. Bennett & D. L. Bassett. 1943. Anesthesiology. **4**: 612.
63. Cournand, A., H. L. Motley & L. Werko. 1947. Federation Proc. **6**: 92.
64. Gibbon, J. H., Jr. & G. J. Haupt. 1955. Surg. Clin. N. Amer. **35**: 1553.
65. Maloney, J. V., Jr., J. O. Elam, S. W. Handford, G. A. Balla, D. W. Eastwood, E. S. Brown & R. H. Ten Pas. 1953. J. Am. Med. Assoc. **152**: 212.

THE EVOLUTION OF CONTROLLED RESPIRATION IN ANESTHETIC PRACTICE

By E. M. Papper

Anesthesiology Service, The Presbyterian Hospital; and the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Controlled respiration is "therapeutic" artificial respiration. The term suggests that failure of spontaneous respiratory activity has been induced and that a new pattern of breathing has been substituted for it. The justification for an induced absence of normal spontaneous respiration and its replacement by an artificial rate and rhythm requires understanding of the physiological changes that are wrought by controlled respiration and the clinical purposes that this method subserves. The good and the bad must be assessed impartially.

In any modern operating room it is not unusual to find controlled respiration practiced as a regular and perhaps routine procedure. An interesting facet of the increased use of controlled respiration by the anesthesiologist is the attitude of the surgeon. One almost never hears any comment on the absence of the sound of breathing. Not too many years ago the surgeon was unhappy unless he could hear the patient breathing. In fact, this desire to hear breathing was carried to the extreme of condoning obstructed breathing because it was noisier and could be heard more easily. Today the quiet or inaudible breathing of properly executed controlled respiration is accepted in most institutions as normal and usual.

It is not my purpose to outline the historical development of this technique. The practice of controlled respiration may be considered to have begun generations ago if the concept of artificial respiration with imposed airway pressures is accepted as a forerunner of this method. It is necessary, however, to look at some aspects of its development. In 1934 Guedel and Treweek[1] published a short paper entitled *Ether Apnoeas*. This report was based on 4 years of clinical observation. They made the point that respiration depends upon receiving an adequate respiratory stimulus and possessing an adequate degree of responsiveness in the respiratory center. In the anesthetized state the center could be depressed by ether and stimulated by carbon dioxide. By use of the to-and-fro absorption method Guedel and Treweek were able to arrange a system that depressed the center by admitting an increment of ether to the brain and that simultaneously reduced the stimulus by efficient absorption of carbon dioxide. This produced apnea of varying duration. The authors made an interesting observation: "With an ether anesthesia technique, in which the blood carbon dioxide and oxygen are under control, respiratory paralysis becomes, not an accident to be shunned, but at times *a favorable circumstance to be encouraged*." These writers then proceeded to consider methods of achieving controlled respiration. In the last paragraph of their paper they de-

fined "the favorable circumstance." "Ether apneas are of no advantage except that they present a quieter abdominal operative field than can be produced with the same ether saturation under other circumstances."

Guedel and Treweek believed that the induction of apnea and artificial respiration by positive pressure was a means of providing greater ease for the surgeon in the form of a quieter abdominal field. They suggested in their paper that such a practice be called "passive respiration," following the suggestion of P. D. Woodbridge. This term never became popular, possibly because of the attitude of the physician practicing the technique. It seemed more dignified and more justifiable to call this practice controlled respiration, thus implying an active decision on the part of the anesthesiologist, rather than passive respiration, which denotes something out of his control and imposed upon him by the patient.

Guedel's work leads us to further examination of the reasons for the use of controlled respiration as a deliberate anesthetic practice. It seems probable that, from the time of Guedel's report until muscle relaxants came into use, the only major reason for using controlled respiration was to secure a quieter field for the surgeon. An unusual exception to this concept was the routine use of controlled respiration by anesthetists who used cyclopropane in the period between 1935 and 1942. Compared with ether, the use of this agent allowed very great speed in intubation and in obtaining a good surgical field. Moreover, the use of controlled respiration effected a partial compensation for cyclopropane's deficiency as a muscular relaxant. However, on closer examination, it appears that in the first years of its modern application the greatest advantage of controlled respiration lay in overcoming the harmful or potentially harmful effects of anesthesia. To achieve good muscular relaxation it was necessary to deepen anesthesia to the point where hypoventilation ensued. Hypoventilation also was the consequence of analgesic premedication. When relaxants came into general use in 1942, they became yet another potential or actual cause of hypoventilation or apnea. In the hands of the scientifically oriented physician, controlled respiration has been a means of overcoming the harmful effects of these agents while preserving at least normal oxygenation of the blood and, in most instances, an efficient excretion of carbon dioxide.

Over the years, several interrelated factors have emphasized the need, or at least the desirability, for controlled respiration: (1) the necessity to overcome the depressant effects of analgesic, anesthetic, and muscle-relaxant drugs; (2) the desirability of providing a quieter field for the surgeon, whether this be in the abdominal cavity or, even more important, in the chest; (3) the inability to produce both a good operative field and effective ventilation without some form of assistance to breathing during general anesthesia; and (4) the increased interest in mechanical ventilators (the use of a mechanical ventilator implies the production of the state of apnea or, at least, of hypoventilation).

Lest the enthusiasm for this form of anesthetic manipulation be exaggerated, we should consider the actual or possible harmful effects of this

practice. The details will be considered by others in this monograph, but I should like to list the general areas in which harm may come through controlled respiration.

The first obvious but often forgotten danger when this method is used with potent anesthetics such as ether, cyclopropane, and chloroform is the very real possibility of producing an effective overdose, resulting in severe myocardial depression and possibly death; in the hands of the inexpert operator this method can bring about cardiac arrest. A second disadvantage is the production of depression of the circulation in patients who have circulatory or respiratory insufficiency. Third, when controlled ventilation is improperly applied, carbon dioxide is not removed effectively, and respiratory acidosis, all the consequences of which are still unknown, ensues.

With regard to future developments, it seems inevitable and, to this observer at least, desirable that the clinical application of controlled respiration will increase. This technique follows on the heels of the increased use of nonpotent gases, intravenous anesthetics, and muscular relaxants. The problem remains as to how most efficiently to ventilate the patients with different types of severe respiratory and circulatory disability. In the case of the patient with healthy lungs, controlled respiration is easy to apply and is well tolerated, but it becomes a very trying and difficult procedure for the patient who is a grave risk. Much more study is necessary to define the limitations and advantages of this technique for patients who are critically ill.

Reference

1. Guedel, A. E. & D. N. Treweek. 1934. Ether apnoeas. Current Researches Analgesia & Anesthesia. **13**: 263–264.

Part III. Fluid and Electrolyte Balance in Surgery

RESPIRATORY ALKALOSIS*

By Kathleen E. Roberts, J. William Poppell, Henry T. Randall, and Parker Vanamee

The Departments of Medicine and Surgery, Cornell University College of Medicine; the Memorial Center for Cancer and Allied Diseases; and the André and Bella Meyer Physiology Laboratory of the Sloan-Kettering Institute, all in New York, N. Y.

An increase in pulmonary ventilation sufficient to cause an excessive loss of carbon dioxide will result in respiratory alkalosis. The initial defect in the plasma is a loss of carbonic acid and a distortion of the bicarbonate: carbonic acid ratio and thus an elevation of blood *p*H. Compensatory alterations occur immediately and cause predictable changes in the remaining electrolytes. The purpose of this paper is to present these metabolic alterations and to express them quantitatively as criteria for diagnosis and therapy.

Initiating Factors

In the absence of metabolic acidosis, any factor that will increase alveolar ventilation may cause respiratory alkalosis. These include both chemical and mechanical factors, and are as follows: salicylate intoxication, lesions of the central nervous system, anoxia, elevated blood ammonium, thyrotoxicosis, fever, infection, certain types of pulmonary disease, high altitude, psychic hyperventilation, and injudiciously administered mechanical ventilation. Occasionally no obvious cause for hyperventilation can be found. The mechanisms whereby lesions of the central nervous system, anoxia, psychic factors, artificial ventilation, and salicylates cause increased ventilation have been well defined. Hyperventilation resulting from certain types of pulmonary disease may be based on pathological disturbances that prevent adequate diffusion of oxygen; in such a case, anoxia, possibly with some contribution from vagal reflexes, is the respiratory stimulus involved. The mechanisms whereby ammonium, thyrotoxicosis, fever, and infection stimulate respiration have not been clearly defined. Regardless of the mechanisms instigating respiratory alkalosis, however, the compensatory alterations are similar, and the signs and symptoms of respiratory alkalosis and of the associated metabolic alterations will be superimposed on those underlying conditions that triggered the hyperventilation.

Plasma Alterations

Abnormal alterations of acid-base equilibrium may affect a variety of buffer systems both inside and outside the cell. Since the bicarbonate buffer system is the one most easily available for analysis, and since it reflects

* The work described in this article was supported by Grant H-1641 from the Public Health Service, National Heart Institute, Dept. of Health, Education, and Welfare, Bethesda, Md.

alterations in other body systems, it is commonly used for establishing a diagnosis. The ratio of bicarbonate to carbonic acid at the normal *p*H of 7.4 in the plasma is maintained at 20:1. Alterations in the content of either bicarbonate or carbonic acid will change the *p*H proportionately. Therefore, analyses of *p*H and of total carbon dioxide and the use of the Henderson-Hasselbach equation permit calculation of either moiety. Commonly, the carbonic acid fraction of the plasma is expressed as the partial pressure of dissolved carbon dioxide (P_{CO_2}) and is used in this text as an index of carbonic acid content of the plasma.

The sequential changes in the bicarbonate buffer system and the various stages of respiratory alkalosis are shown diagrammatically in FIGURE 1. During the initial stage of respiratory alkalosis the loss of carbonic acid without an equivalent loss of bicarbonate disturbs the normal 20:1 ratio, and the *p*H will increase. The plasma bicarbonate content represents the major fraction of the total carbon dioxide, as analyzed in the plasma; since this fraction is only slightly altered initially, the total carbon dioxide will be minimally decreased. Metabolic compensations occur rapidly, however, and eventually they lead to a decrease in the bicarbonate as well as in the carbonic acid fraction. At least 3 anions—chloride, ketones, and lactic acid—have been shown to increase in respiratory alkalosis. The elevation in chloride is due to a shift from the red cells and, possibly, from other undetermined sources. Lactic acid is formed from the breakdown of glycogen and other intermediate products of carbohydrate metabolism. Ketone acids sometimes increase, and they are also the result of defective carbohydrate metabolism. The endogenous invasion of these anions displaces the extracellular base-bound bicarbonate, and the bicarbonate thus converted to carbon dioxide by titration is excreted by the lungs. The net result is a significant decrease in the bicarbonate content of the plasma. By this means the bicarbonate:carbonic acid ratio tends to be restored toward the normal value of 20:1, and extreme changes in *p*H are minimized. If this process occurs to such an extent that the *p*H is restored to normal, the situation is termed "compensated respiratory alkalosis." As the metabolic compensations continue, the majority of the extracellular bicarbonate may be lost, and the end stage of respiratory alkalosis is recognized as a metabolic acidosis, in which there is a drop in *p*H, in bicarbonate, and in carbonic acid. These 3 stages are not clear-cut: the degradation from one to another is gradual and there may be a considerable overlap.

The 3 stages of respiratory alkalosis are shown in TABLE 1 for 3 patients. The first patient had a typical chemical picture of respiratory alkalosis, with

TABLE 1

PLASMA ELECTROLYTES IN 3 PATIENTS DEMONSTRATING THE 3 STAGES OF RESPIRATORY ALKALOSIS

	Na	K	Cl	CO_2	*p*H
Uncompensated respiratory alkalosis.....	143	5.2	112	25	7.52
Compensated respiratory alkalosis.....	122	5.3	100	16	7.42
Severe end-stage respiratory alkalosis.....	145	4.5	131	6	7.11

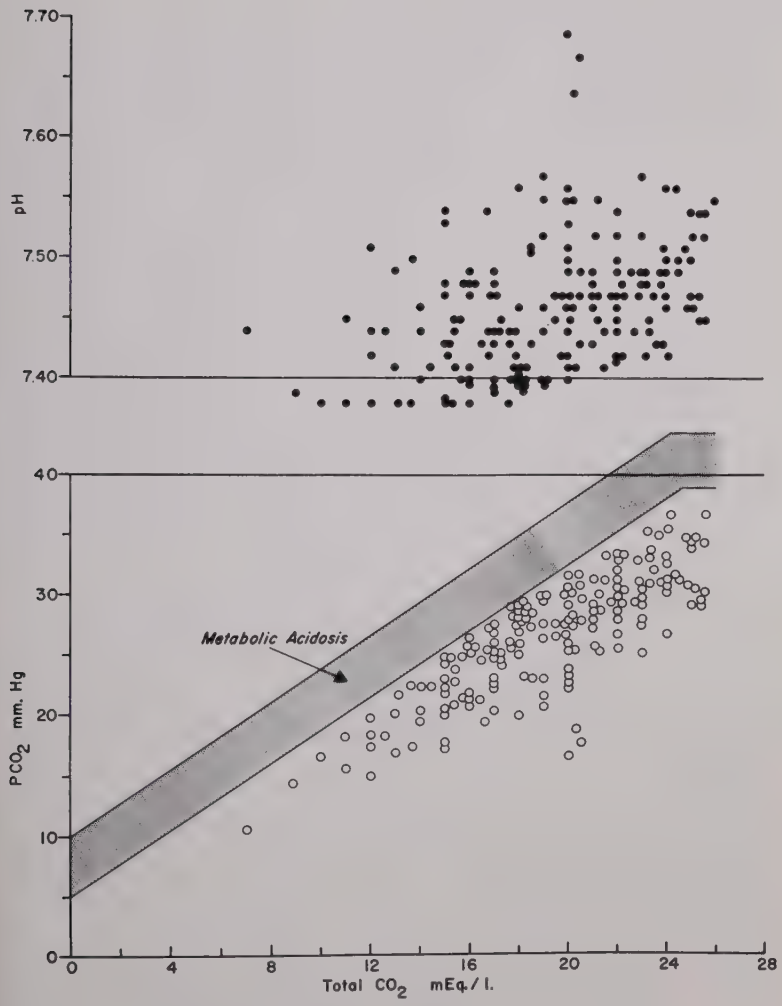

FIGURE 1. The 3 stages of respiratory alkalosis.

elevated *p*H and slightly decreased plasma carbon dioxide. The second patient had a compensated respiratory alkalosis, as shown by the normal *p*H and lowered carbon dioxide content of the plasma. The third patient displayed the end result of respiratory alkalosis, and the diagnosis could not be distinguished from metabolic acidosis except by his history and by the progression of plasma chemical findings.

In assessing the compensations in acid-base disturbances it is significant that respiratory alkalosis can be completely compensated by metabolic means, in contrast to metabolic acidosis, which can be only partially compensated by respiratory means. This difference is illustrated in FIGURE 2, which shows that respiratory alkalosis, even when compensated, can easily be differentiated from metabolic acidosis. In metabolic acidosis the base-bound bicarbonate, one of the major extracellular buffers, titrates the invading acid, forming carbon dioxide and water. The increase in respiration that occurs in metabolic acidosis dispenses the carbon dioxide so released, and the *p*H as well as the amounts of bicarbonate and carbonic acid in the plasma decrease accordingly. This process whereby bicarbonate is lowered in metabolic acidosis is not dissimilar, qualitatively, from that observed in respiratory alkalosis. However, there is a significant quantitative difference, which is illustrated in FIGURE 2. In patients with metabolic acidosis it has been found that the *p*H is usually decreased when the content of carbon dioxide in the plasma is lower than 20 to 22 mM/l. and, for any given change in carbon dioxide, there is a predictable lowering of the P_{CO_2} that is always quantitatively different from that observed in respiratory alkalosis. The changes in P_{CO_2} in patients with metabolic acidosis are shown by the enclosed stippled area, which demonstrates the range of P_{CO_2} that occurred

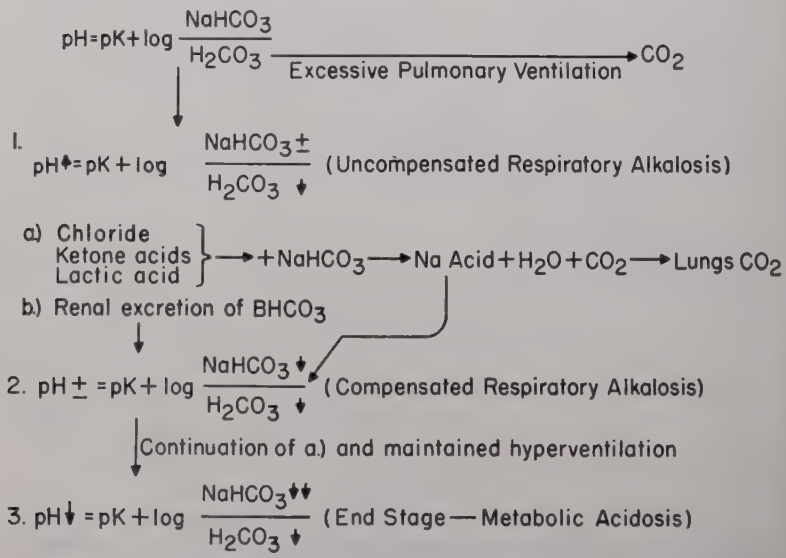

FIGURE 2. Upper part of figure: blood *p*H values in patients with respiratory alkalosis (solid circles). Lower part of figure: comparison of plasma P_{CO_2} (open circles) in patients with respiratory alkalosis and in patients with metabolic acidosis (stippled area). The P_{CO_2} and *p*H are plotted in relation to total carbon dioxide content in the plasma.

at any given total carbon dioxide content of the plasma. The open circles represent the plasma P_{CO_2} in patients with respiratory alkalosis. As the figure shows, at any given concentration of carbon dioxide these patients displayed a lower P_{CO_2}, and hence a greater alveolar ventilation, than did patients with metabolic acidosis. This chart also demonstrates that the *p*H of patients with respiratory alkalosis was normal only when the total carbon dioxide content had decreased to less than 18 mM/l. and, even then, *p*H was normal only in a minority of patients. From this chart it can be seen that a patient displaying a low P_{CO_2} that is below the limits imposed by metabolic acidosis will have a respiratory alkalosis. However, as respiratory alkalosis progresses and titration of bicarbonate continues, the chemical findings in the plasma will be indistinguishable from those of metabolic acidosis; hence, the diagnosis of the late stage of respiratory alkalosis cannot be made from this chart.

Renal compensations in respiratory alkalosis have been described, but they are much less effective than those accomplished by metabolic means. It has been shown that in acute respiratory alkalosis the reabsorption of filtered bicarbonate is decreased and that bicarbonate excretion is increased. However, this effect of respiratory alkalosis on renal bicarbonate absorption can be more clearly demonstrated in bicarbonate-loaded animals than in patients with respiratory alkalosis who are not receiving bicarbonate. The loss of extracellular bicarbonate by renal excretion is, in fact, minimal, and urinary losses may account for less than 1 to 5 per cent of that lost from the extracellular fluid. Furthermore, the effects of respiratory alkalosis on renal reabsorption of bicarbonate are only partially inhibitory, and the reabsorption of filtered bicarbonate may be decreased to only 18 to 22 mEq./l. of glomerular filtrate. In addition, there is often intracellular compensation and an associated intracellular potassium deficit; then, because the loss of this intracellular cation tends to counteract the effects of respiratory alkalosis, bicarbonate reabsorption may be normal. For these reasons a patient would not be expected to excrete bicarbonate under the following conditions: if the respiratory alkalosis were not acute and intracellular compensations had occurred; or if there were a superimposed potassium depletion; or if the plasma carbon dioxide content were below 18 to 20 mEq./l. Therefore, we have rarely observed excretion of any significant amounts of bicarbonate, and the urine is most frequently acid in respiratory alkalosis except in the very acute early stages, or when patients were given excessive potassium replacement.

Intracellular Compensations

The total loss of carbon dioxide from the body in respiratory alkalosis is known to be greater than can be accounted for by losses from the extracellular fluid. This can be demonstrated by measurements of the amount of oxygen consumed and of carbon dioxide lost; the carbon dioxide lost in excess of the oxygen consumed corresponds to a respiratory quotient greatly

in excess of 1.0. The carbon dioxide lost in excess of the oxygen consumed represents the amount of carbon dioxide that is in excess of that metabolically produced, and therefore must have been released from body stores. Since the excess of carbon dioxide may also be greater than could be accounted for by extracellular sources of both bicarbonate and carbonic acid, some of it undoubtedly represents losses of intracellular bicarbonate and carbonic acid. The loss of intracellular bicarbonate has been postulated to be a result of titration of intracellular bicarbonate by lactic acid and of diffusion of the intracellular carbonic acid so formed to the extracellular compartment. This process would therefore serve to lower both intracellular bicarbonate and carbonic acid, and it would, of course, tend to restore the intracellular compartment to a state of compensation.

Although most of the carbon dioxide lost from the lungs in respiratory alkalosis can be accounted for by estimated intracellular and extracellular stores, there is another smaller moiety that does not come from these sources. This discrepancy can be demonstrated for the entire organism or for an individual organ such as the kidney. Experiments carried out by Irving *et al.*[5] have failed to show that this extra source of carbon dioxide is bone, muscle, or viscera. It seems likely, therefore, that the excess carbon dioxide may result from metabolic degradation of glycogen or glycogen precursors. It has been shown that animal tissues are capable of fixing carbon dioxide and of incorporating it into the citric acid cycle and thus into glycogen. Since this is a reversible reaction, the withdrawal of carbon dioxide from tissues that occurs in respiratory alkalosis[4] might be expected to result in glycolysis and the release of lactic acid and carbon dioxide*. Thus carbohydrate metabolism may be impaired. Furthermore, it has been shown that insulin is *p*H-sensitive and that alkalosis may affect its action. These two defects may account in part for the elevation of lactic acid and the occasional formation of ketone acids in respiratory alkalosis. It has also been suggested that dissociation of oxyhemoglobin might be impaired in respiratory alkalosis and that tissue anoxia would cause elevation of lactic acid as a result of anaerobic metabolism. This factor, although possibly contributory, has not been definitely clarified, and there is evidence that unloading of oxygen to the tissues, as discussed below, is not a serious defect in respiratory alkalosis.

Alterations in Other Electrolytes

The concentrations of potassium and sodium in the extracellular fluid are known to decrease in respiratory alkalosis as a result of either intracellular shifts or increased renal excretion. Phosphate also has been shown to decrease, largely as the result of intracellular shifts. Changes in total and in ionized calcium have been reported, but the confirmatory evidence has been inconsistent.

* It has been suggested by J. A. Jacquez[6] that the dynamics of this reaction are such that the release of CO_2 could occur if glycogen were converted to fat in respiratory alkalosis.

Neurological Changes

The neurological and mental changes observed in respiratory alkalosis consist of: dizziness, tinnitus, paresthesias, slurring of speech, disorientation, and peripheral neurological changes, including positive Babinski's reflex, flapping tremor, clonus, and painful plantars. The neurological changes are characteristically transient and shifting, and they have been ascribed to a variety of factors. It has been postulated that oxygen unloading to the tissues may be impaired because of the Bohr effect. This hypothesis has been challenged, however, because (1) decreased cerebral oxygen consumption has not been found in respiratory alkalosis; and (2) defective oxygen unloading to the myocardium cannot be clearly shown to be the cause of the electrocardiographic changes associated with respiratory alkalosis. It has also been postulated that there is a decrease in ionized calcium. However, proof of this is lacking, and the reversal of the neurological changes by the administration of calcium is not consistently accomplished, either clinically or experimentally. It is possible that the mental and peripheral neurological changes are partially the result of cerebral vasoconstriction, which has been demonstrated in patients in experimentally induced hyperventilation.

Differential Diagnosis

The condition that is most often confused with respiratory alkalosis and has most often resulted in mistaken diagnosis is metabolic acidosis. In both conditions there is a decrease in carbon dioxide and the patients may show some degree of hyperventilation. In both hyperchloremic acidosis and respiratory alkalosis an elevation of the plasma chloride often accompanies the decrease in carbon dioxide and may lead to confusion. Diabetic acidosis, frequently characterized by acetonuria, may be imitated by respiratory alkalosis, which is occasionally accompanied by acetonuria. The differentiation of respiratory alkalosis and metabolic acidosis may be resolved by measuring the *p*H and carbon dioxide content of the blood and by calculating the P_{CO_2} (FIGURE 2). However, since *p*H determinations may be difficult to obtain, this is often impossible; and, unless the measurement is carried out meticulously by a highly skilled technician, the *p*H may be dangerously misleading.

The similarity of the plasma electrolytes in respiratory alkalosis and metabolic acidosis is clearly illustrated in TABLES 2 and 3. In TABLE 2 the concentrations of chloride, carbon dioxide, and other electrolytes in the plasma of a patient with respiratory alkalosis are compared with those of a patient with hyperchloremic acidosis due to chronic renal disease. Both patients displayed hyperchloremia, a decreased plasma carbon dioxide, and similar concentrations of sodium and potassium. The *p*H in the 2 patients, however, was quite dissimilar and established the diagnosis. In TABLE 2 are also shown 2 other patients with similar electrolyte alterations and in whom the *p*H alone was dissimilar. TABLE 3 shows that respiratory alka-

TABLE 2

A COMPARISON OF PLASMA ELECTROLYTES OF PATIENTS WITH RESPIRATORY ALKALOSIS AND METABOLIC ACIDOSIS

	Sodium mM/l.	Potassium mM/l.	Chloride mM/l.	Carbon dioxide mM/l.	pH	P_{CO_2} mm. Hg
Patient 1 (Respiratory alkalosis)	143	4.6	116	22	7.52	27
Patient 2 (Hyperchloremic acidosis)	132	4.2	116	23	7.32	43
Patient 3 (Respiratory alkalosis)	122	5.9	97	14	7.50	18
Patient 4 (Metabolic acidosis)	117	5.9	93	15	7.27	32

losis may, in some cases, be confused with diabetic acidosis. The patient, who was receiving a 10 per cent glucose solution administered rapidly and intravenously, displayed ketonuria and glycosuria, and he was in deep coma. However, on the basis of determinations of pH and ammonia, it was shown that the patient had severe respiratory alkalosis due to an elevated blood ammonium concentration. Therapy with sodium glutamate and carbon dioxide resulted in complete recovery of this patient and supported the diagnosis.

Although the differential diagnosis between respiratory alkalosis and metabolic acidosis can be established with complete certainty in the early stages of these conditions, provided that an estimate of pH is available, the terminal stage of respiratory alkalosis may still be confused with metabolic acidosis. Other factors that may aid in establishing the diagnosis are outlined in TABLE 4. The most important differences are the neurological and mental changes usually found in respiratory alkalosis but rarely observed in metabolic acidosis except in renal disease. FIGURE 2 shows that for any given change in carbon dioxide content of the plasma, the P_{CO_2} is greater in patients with metabolic acidosis than in patients with respiratory alkalosis. This finding indicates that there is a greater stimulus to respiration and thus a greater increase in alveolar ventilation and in subsequent loss of carbon dioxide in patients with respiratory alkalosis than in metabolic acidosis. This can often be detected clinically: the increase in respiration accompanying metabolic acidosis is usually less obvious than that displayed

TABLE 3

PLASMA ELECTROLYTES BEFORE AND AFTER TREATMENT BY SODIUM GLUTAMATE OF A PATIENT WITH HEPATIC COMA FROM ELEVATED BLOOD AMMONIUM

	Plasma				Urine		
	CO_2 mEq./l.	pH	K mEq./l.	Sugar mg. %	Acetone	Sugar	
Before treatment (Nov. 26)	20	7.69	2.4	212*	3+	2+*	Hepatic coma
After treatment (Nov. 28)	21	7.4	2.7	97	0	0	Out of coma

*Patient receiving 10 per cent glucose when this determination was made.

Table 4

Comparison of Clinical and Chemical Change in Patients with Metabolic Acidosis and Respiratory Alkalosis

	Respiratory alkalosis	Metabolic acidosis
*p*H early	↑	↓
*p*H compensated	±	
*p*H late	↓	
CO_2	↓	↓
Cl	↑ → ±	↑ → ±
K	↓ ±	↑ ± ↓
PO_4	↓ ±	↑ ↑ ±
Pulmonary ventilation	↑ ↑ ↑	↑
Neurological changes	↑	Rare except in renal failure

by the patient with respiratory alkalosis, although both types of patients will have an increased alveolar exchange. A decrease in plasma potassium and phosphate and an elevation of plasma chloride are common, but not consistent, findings in clinical cases of respiratory alkalosis. Although changes in the amounts of these ions in plasma may aid in establishing a diagnosis, this basis is not entirely reliable, since associated renal, hepatic, or cardiac disease is often superimposed on respiratory alkalosis and may influence the expected alterations.

Treatment

The treatment of respiratory alkalosis should be aimed at the correction of the precipitating causes and of the electrolyte alterations. Early phases of respiratory alkalosis may be treated by administering 5 per cent carbon dioxide intermittently by face mask. Since this is often intolerable to the patient, however, a nasal catheter or a tent may be employed instead. If these are used, 10 per cent carbon dioxide is more effective than 5 per cent in correcting the altered *p*H and P_{CO_2}. When hypokalemia or hypophosphatemia is present, potassium or phosphate should be given, either intravenously or orally. If the respiratory alkalosis has been of such duration and severity that metabolic acidosis has occurred, or if the total carbon dioxide content of the plasma is less than 12 to 14 mM/L., sodium bicarbonate may be given at the time the patient is placed in an atmosphere of carbon dioxide. Since lactic acid is already present in excessive quantities, the administration of sodium lactate is often futile.

In administering sodium bicarbonate to patients with end-stage metabolic acidosis it is important to recognize that, if the stimulus to increased respiration has not been removed, the exogenously administered bicarbonate will be titrated by the patient's own lactic acid, chlorides, and ketones, in a manner similar to that in which the extracellular bicarbonate has already been titrated. Therefore, much greater quantities of sodium bicarbonate are required to correct the abnormal plasma carbon dioxide of patients with respiratory alkalosis than are usually required to correct a comparable decrease of carbon dioxide in metabolic acidosis. When the end stage of

respiratory alkalosis is associated with intoxication from an elevated concentration of ammonium in the plasma, sodium glutamate, and not sodium bicarbonate, should be administered. Sodium glutamate serves a dual purpose: the glutamate decreases blood ammonium by forming glutamine, which is metabolized, thereby removing the stimulus to respiration; and the sodium administered with the glutamate provides for the necessary bicarbonate by correcting the lowered carbon dioxide. Therefore, the administration of sodium bicarbonate, as such, is not necessary if the respiratory alkalosis is associated with ammonium intoxication.

Summary

In the absence of metabolic acidosis, an increase in pulmonary ventilation sufficient to discharge more than normal amounts of carbon dioxide from the lungs will result in a respiratory alkalosis. There are 3 major stages of respiratory alkalosis: (1) the initial stage, which is characterized by an elevated blood *p*H and a minimal lowering of carbon dioxide in the plasma; (2) the second stage, characterized by a further decrease in total carbon dioxide of the plasma, in which the *p*H may be normal (this stage has been termed "compensated respiratory alkalosis"); (3) the end stage of respiratory alkalosis, a metabolic acidosis that results from excessive loss of bicarbonate due to endogenous acid formation. The elevation of the concentrations of lactic acid, chloride, and occasionally ketone acids in the plasma is primarily responsible for the titration of extracellular sodium bicarbonate and thus for compensating respiratory alkalosis. Associated electrolyte alterations that are commonly seen in respiratory alkalosis include hypokalemia, hypophosphatemia, and hyperchloremia. It has been postulated that there are intracellular as well as extracellular losses of bicarbonate and carbonic acid in respiratory alkalosis. There may also be disturbances of carbohydrate metabolism. The differential diagnosis between metabolic acidosis and respiratory alkalosis has been outlined and the treatment of respiratory alkalosis has been indicated.

Acknowledgment

The authors are indebted to the following investigators for permission to quote from their unpublished observations: Harry N. Bane, Fidel Cuajunco, Jr., Jerome J. DeCosse, George Firmat, J. Shelton Horsley, III, Walter Lawrence, Jr., and Arthur E. Schwartz.

References

1. Bock, A. V., H. Field, Jr. & G. S. Adair. 1924. Oxygen and carbon dioxide dissociation curves of human blood. J. Biol. Chem. **59:** 353.
2. Brazeau, P. & A. Gilman. 1953. Effect of plasma CO_2 tension on renal tubular reabsorption of bicarbonate. Am. J. Physiol. **175:** 33.
3. Brown, E. B. Jr. 1953. Physiological effects of hyperventilation. Physiol. Revs. **33:** 445.

4. Carryer, H. M. 1947. Tissue anoxia resulting from respiratory alkalosis. Proc. Staff Meeting Mayo Clinic. **22**: 456.
5. Irving, L., J. K. W. Ferguson & F. W. Plewes. 1930. The source of CO_2 expired and the site of its retention. J. Physiol. **69**: 113.
6. Jacquez, J. A. Personal communication.
7. Perry, F. A., H. T. Randall, J. W. Poppell & K. E. Roberts. 1956. Blood volume replacement in surgical patients. Surg. Clin. N. Amer. **36**: 301.
8. Peters, J. P. & D. D. Van Slyke. 1946. Quantitative Clinical Chemistry. Interpretations. **I**. 2d ed. Williams and Wilkins. Baltimore, Md.
9. Pitts, R. F. 1953. Mechanisms for stabilizing the alkaline reserves of the body. The Harvey Lectures 1952–1953: 172. Academic Press. New York, N. Y.
10. Poppell, J. W., P. Vanamee, K. E. Roberts & H. T. Randall. 1956. The effect of ventilatory insufficiency on respiratory compensation in metabolic alkalosis. J. Lab. Clin. Med. **47**: 885.
11. Relman, A. S., B. Etsten & W. B. Schwartz. 1953. Regulation of renal bicarbonate reabsorption by plasma carbon dioxide tension. J. Clin. Invest. **32**: 972.
12. Roberts, K. E., H. T. Randall, H. L. Sanders & M. Hood. 1955. The effects of potassium on renal tubular reabsorption of bicarbonate. J. Clin. Invest. **34**: 666.
13. Roberts, K. E., G. Thompson, J. W. Poppell, H. T. Randall & P. Vanamee. 1957. Respiratory alkalosis accompanying ammonia toxicity. J. Appl. Physiol. **9**: 367
14. Roberts, K. E., P. Vanamee, J. W. Poppell, A. Rubin, W. Braveman & H. T. Randall. 1956. Electrolyte alterations in liver disease and hepatic coma. Med. Clin. N. Amer. **40**: 901.
15. Vanamee, P., F. Cuajunco, Jr., H. T. Randall & K. E. Roberts. 1956. Additive effects of respiratory alkalosis, carbonic anhydrase inhibition and potassium on renal tubular reabsorption of bicarbonate. Abst. Federation Proc. **15**: 190.
16. Vanamee, P., J. W. Poppell, A. S. Glicksman, H. T. Randall & K. E. Roberts. 1956. Respiratory alkalosis in hepatic coma. Arch. Internal Med. **97**: 762.
17. Welt, L. G. 1955. Clinical Disorders of Hydration and Acid Base Equilibrium. 1st ed. Little, Brown & Co. Boston, Mass.

SPECIAL PEDIATRIC PROBLEMS IN FLUID AND ELECTROLYTE THERAPY IN SURGERY

By Jerome S. Harris

Departments of Pediatrics and Biochemistry, Duke University School of Medicine, Durham, N. C.

In his book, *The Surgery of Infancy and Childhood,* Robert Gross states: "In a book on pediatric surgery, the most difficult chapter to write is that concerning preoperative and postoperative care."[1] Such care, although based on scientific principles, represents an art that cannot be reduced to formulae, but must be adjusted to the nature and proportions of each child; one that must be sensitive to the rapid changes in his reactions; and one that must be attuned to the physiological alterations that may signify serious difficulties. In the special problems attending fluid and electrolyte balance, this art must be individualized in its expression for each child and exercised with a constant and compulsive attention to details.

Lest this appear too discouraging, the situation is simplified by a number of factors for which pediatricians can be most grateful. Most children need no special preoperative or even postoperative care. They seldom have chronic or degenerative diseases of the heart, lungs, or kidneys. Given half a chance, they possess an enormous capacity for recovery. Postoperative nausea and vomiting are usually of short duration; spontaneously or with only slight urging, the child will take fluids that he likes. His spontaneous movements shorten convalescence and prevent postoperative complications.

In fluid and electrolyte therapy in pediatric surgery the first problem of the physician is to learn to exhibit watchful inactivity and to refrain from useless or harmful interference: from giving parenteral fluids when oral fluids are accepted; from damaging the child's incredible recuperative powers by subjecting him to an unnecessary infusion; from loading him with salt; from drowning his tissues with water; from exposing him to the hazard of serum hepatitis by unnecessary transfusions; from upsetting him by unnecessary separation from his mother; from frightening him by talking about gas and by using masks and complicated apparatus; and, finally, by leaving him for an unnecessarily long period of time in a recovery room that may appear to him as a chamber of horrors.

In general, the special problems of fluid and electrolyte therapy in infants and children are based on: (1) their small size; (2) the variation in the ratio of surface area to weight as size diminishes; (3) the effects of growth and the immaturity of systems and organs; (4) the nature of the child's reactions; and (5) the peculiarities of the premature and newborn infant.

The difference in size alone presents a real problem in therapy. I need not remind anesthetists of this fact. In the newborn child, anesthetists deal with a tidal air of approximately 6 cc./kg. and must devise special apparatus and techniques to minimize the dead space. The surgeon is also aware of a blood volume of approximately 80 cc./kg. (a total of only

250 to 300 cc. in the newborn infant); a stroke volume of 4 cc./kg.; and a minute volume that is much greater than the total blood volume. A loss of 1 oz. of blood in the newborn corresponds to the amount of a full transfusion in adults. The volumes of the various fluid compartments (extracellular and intracellular fluid, and blood volume) and the total amounts of various materials in the body bear a fairly direct relationship to weight—although their turnover rates may not do so. Losses and replacements of these substances should therefore be scaled to weight and administered on a per kilogram basis. For this reason any loss of blood must be magnified ten- to twentyfold for the infant as contrasted to the adult. Similarly, fluids administered for *replacement* must be also adjusted to weight. Incidentally, the ease of handling children and the fact that measurements of weight can be made with a high degree of accuracy make weight one of our best guides in therapy—one that is unfortunately too frequently neglected. For example, dehydration usually involves a loss of 10 per cent of the infant's body weight. This is largely a loss in water, and a replacement of 100 cc. of fluid per kilogram should be alloted. The type of fluid to be administered depends upon the losses that have been sustained. Fortunately, the composition of the fluid loss in many clinical conditions (diarrhea, pyloric stenosis, and even diabetic acidosis) does not vary far from a sodium content of 60 mEq./l., chloride of 50 mEq./l., and potassium of 30 mEq./l.[2, 3] Solutions with similar concentrations of ions have been devised and are available commercially. They may be added in appropriate amounts to the total daily fluid intake *after* renal function has been established by the administration of saline, plasma, or blood.

It should be remembered that a liter of fluid, which may be a suitable quantity for an adult who needs rapid refilling of the extracellular fluid compartment, must be reduced by one tenth or one twentieth for the infant. It is not too unusual to see a liter or half-liter bottle attached to an intravenous set for an infant. This is equivalent to suspending a 5-gallon carboy over an adult and threatening to flood his tissues with its contents. In the infant all volumes should be selected in proportion to the weight of the child. No more than one half of the total daily fluid requirements should be placed in an intravenous set at any one time. This will ensure that the child will never be flooded, and that the staff will make very certain that the rate of administration is sufficiently slow to make the drip continuous and to obviate the necessity for frequent replacement into the vein. In this manner the fluids will be given at the rate for maximal benefit by the infant.

The small size of the infant makes the administration of subcutaneous fluids doubly dangerous. It is simple to give the complete daily supply of fluids at one time by subcutaneous administration into a number of areas. Since considerable time is required for absorption, the salts of the body may diffuse into these subcutaneous depots and may cause severe salt depletion and dehydration before the fluid is absorbed. Hyaluronidase, although it disperses the fluid and makes it less prominent in the subcutaneous spaces, does not prevent dehydration or salt depletion.

The ease of handling an infant or a child may tempt us to overtreat him. He has a definite need to be left alone. Unless restrained or paralyzed, he will indulge in the correct amount of activity by himself. Let me refer you to Gulliver in Brobdingnag and suggest the comparable picture of a sick adult being handled, turned, and suddenly elevated 20 feet into the air by 24-foot giants weighing perhaps 4000 pounds.

The reduction of an adult to a Lilliputian form is more complex than an equal scaling down of all dimensions. Let us consider these general phenomena as discussed so eloquently by D'Arcy Wentworth Thompson in his book *On Growth and Form*[4] and determine whether an understanding of them will aid us in the therapy of children. Simply stated, the rules governing similar figures are: the surface area increases as the square of the linear dimensions, and volume increases as the cube.

$$\text{surface area} \propto \text{length}^2$$
$$\text{volume (weight)} \propto \text{length}^3$$
and
$$\frac{\text{surface}}{\text{weight}} \propto \frac{1}{\text{length}}$$

That these rules hold true to a fair degree in humans is demonstrated in TABLE 1. Note how much more closely the changes in square root of surface area and in the cube root of weight (rather than the actual surface area or weight) follow the changes in length.

These changes have been illustrated schematically in FIGURE 1. The largest figure represents the standard adult. In terms of height the newborn infant is 1/3.3 of the size of an adult. However, in terms of surface area he is 1/9 of the adult size, and in terms of weight he is 1/20 of the adult size. We cannot scale any function from the adult down to the infant or child unless we adjust the scaling to the proper dimension. Thus we cannot scale down the shoe size (a length dimension) according to the proportions of body weight. According to weight proportions, the infant would wear a shoe one twentieth that of the adult size (a little more than one half in. in length), whereas the actual length of the newborn infant's foot is about 3 in.—approximately in the same relationship to the adult foot as the infant's height is to that of the adult. Nevertheless we frequently have been guilty of adjusting therapy to weight by giving drugs on a per kilogram basis when, perhaps, they should have been reduced accord-

TABLE 1

RELATIONSHIP OF LENGTH, SURFACE AREA, AND WEIGHT AT DIFFERENT AGES

Age yr.	Length cm.	Surface area sq. m.	Weight kg.	Ratio to that present at birth: Length	Surface area: S. A.	Surface area: $\sqrt{S.A.}$	Weight: Wt.	Weight: $\sqrt[3]{Wt.}$
Birth	52	0.2	3.1	1.0	1.0	1.0	1.0	1.0
9	126	1.0	29.0	2.4	5.0	2.2	9.4	2.1
18	172	1.73	63.0	3.3	8.7	2.9	20.3	2.7

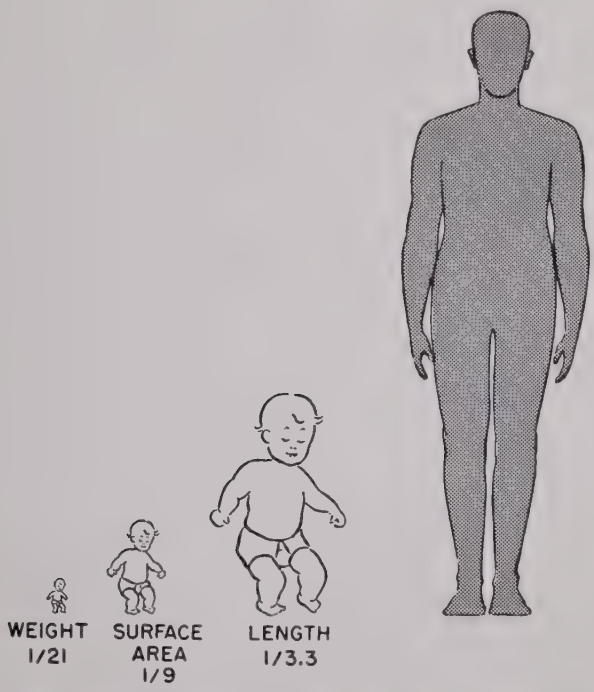

FIGURE 1. Proportions of newborn to adult with respect to weight, surface area, and length.

ing to another dimension. For example, heat losses depend upon surface area (since heat is lost primarily through the surface) rather than upon weight or height. In the same category are metabolism, caloric requirements, turnover rates, insensible perspiration, respiration, and all functions and drugs that are dependent upon any of the preceding factors. Since the ratio of surface area to weight varies inversely to the length, surface area becomes disproportionately large compared to weight as the length of the individual becomes smaller. The infant therefore has a much greater surface area than would be expected from his weight. The anesthetist is quite aware of the resulting relative increase in respiration and metabolism, since he may have much more trouble with oxygenation, hypercapnia, and elimination of dead space in the small infant.

As a general rule, all rates are related to surface area. Whenever the terms per day, per hour, or per minute appear, it is likely that the quantity is a measure of turnover or metabolism, and it is best expressed in terms of surface area. For example, the usual fluid requirement can be given as

TABLE 2

MINIMAL WATER REQUIREMENTS AT VARIOUS RENAL CONCENTRATING ABILITIES*

Urine sp. gravity	Infant 3 kg.	Adult 70 kg.	Infant 0.2 sq. m.	Adult 1.73 sq. m.
1.005	171 cc./kg.	71 cc./kg.	2500 cc./sq. m.	2800 cc./sq. m.
1.015	114 "	46 "	1700 "	1900 "
1.025	94 "	38 "	1400 "	1500 "

* After Darrow.[6]

1500 cc. per sq. m. per day* for practically all sizes[5] (except the premature infant). These requirements are, however, only indirectly related to height or weight and therefore must be varied for each change in these scales: for example, 100 to 150 cc. per kg. per day intake for a 5-kg. child, as compared to 20 to 40 cc. per kg. for the 70-kg. adult. In contrast, TABLE 2 demonstrates how the varying fluid requirements for different ages are made almost identical by expression in terms of surface area, even in the presence of similar disturbances in renal function. Similarly, TABLE 3 shows that the graph given by Gross[1] for the minimal fluid requirements for children weighing 5 to 60 lb. can be more simply expressed by the one figure of 1500 cc./sq. m.†

Surface area can be determined readily from tables (TABLE 4) or nomograms.[7]

The composition of the fluid is determined by the maintenance requirements, which are approximately 30 mEq. sodium (200 cc. isotonic saline), 25 mEq. potassium (2 gm. potassium chloride), 25 mEq. chloride, and 75 gm. carbohydrate (to abolish ketosis) per square meter per day. It is common practice to dissolve these amounts in one liter rather than in 1500 cc. so that $1\frac{1}{2}$ times the minimal requirement is given in the 1500

TABLE 3

MAINTENANCE FLUID REQUIREMENTS* RECALCULATED FOR SURFACE AREA

Weight lb.	Fluid cc.	Recalculated for sq. m.
5	260	1600
10	400	1650
20	650	1500
30	850	1500
40	1050	1500
60	1450	1500
Premature	Preset limit of 30 cc./lb.	
2	60	700
3	90	800

* Gross.[1]

* This figure and the ion requirements are 50 to 70 per cent higher than the basal needs, since allowances have been made for moderate activity, sweating, and urine dilution. The requirements are increased 50 to 100 per cent by high fever, by respiratory overventilation, or by sweating in a hot humid atmosphere or under drapes in an operating room.

† Incidentally, the figure for premature infants, which is roughly one half of the 1500 cc./sq. m., may result in part from their unusually low metabolic rate—also roughly one half of that expected from their body surface area.

Table 4

Surface Area According to Age and Weight

Age	Weight kg.	Weight lb.	Surface area sq. m.
Premature	1.0	2.2	0.1
Premature	2.0	4.4	0.15
Newborn	3.0	6.6	0.20
3 mo.	5.0	11.0	0.25
1 yr.	10.0	22.0	0.45
3.5 yr.	15.0	33.0	0.60
5.0 yr.	20.0	44.0	0.80
9.0 yr.	30.0	66.0	1.05
15.0 yr.	50.0	110.0	1.50
Adult	70.0	154.0	1.75
Adult	90.0	198.0	1.95

cc./sq. m. This load does not tax the normal kidney and allows it to retain ions to compensate for unrecognized losses and deficits.

There is a simpler method of calculating these values. The average adult has a surface area of 1.73 sq. m. and the same solutions can be used and the rates multiplied by 0.58 (0.6 for simplicity) to give the rates per square meter. Thus the values of 2500 ml. fluid, 40 mEq. potassium, and 3 gm. salt daily, suggested for the normal adult, will give, when multiplied by 0.6, the same figures per square meter that we have just recommended for children. Additions of water to compensate for increased insensible losses from the respiratory tract, or of saline for losses by sweating, could be made by using the same rules as for adults and by multiplying by 0.6 to get the rates per square meter, since these losses depend upon surface area.

Suitable surface area-weight-height nomograms should be printed on the back of anesthesia charts. The weight and height could be marked and a line drawn to show the surface area. The requirements per day for all ages (save the premature) could be scaled quickly to the surface area, while the replacement of losses could be scaled to the weight, using 70 kg. as the weight of the standard adult. Continuing losses through suction or from fistulae naturally are calculated on the basis of the actual measured fluid losses. This system would also ensure the proper rates of administration since comparable volumes would be given within comparable times. A transfusion of 10 cc. per kilogram should ordinarily be given in 1 hour regardless of whether 50 cc. of blood is given to a 5-kg. child or 500 cc. to a 50-kg. adult. It is convenient to remember that the day has 1440 minutes. A rate of 1 cc./sq. m./min. will give the maintenance requirement of 1500 cc./sq. m./day.

Therapy in children, however, involves more than a reduction of adult doses to a proper scale—even when a slide rule, exponential functions, and some solid geometry are included in the calculations.

The second major difference between children and adults lies in the capacity to grow, develop, and mature. Maturation does not necessarily parallel age, weight, height, or even surface area, but differs for each individual organ and system.

For example, renal function is underdeveloped until the age of 6 months to 2 years, at which time it reaches adult standards in relation to surface area.[8] Thereafter special consideration need not be given to normal renal function, since the calculations of fluid, electrolytes, and many drugs are already scaled to surface area. Below that age, however, it must be remembered that both glomerular and tubular functions are 20 to 40 per cent less than would be expected from the surface area. In addition, the very young infant and the premature infant show a relative inability to concentrate urine.[9] The maximal osmolarity of urine that can be achieved in the first few weeks is only 700 mOs. per liter, in contrast to the adult maximum of 1400 mOs. per liter. More water is therefore required to eliminate metabolites, particularly during periods of increased metabolism as in fever, infections, and other states of increased tissue breakdown (for example, after surgery) where greater numbers of osmotically active substances must be excreted. Since the ability to dilute the urine remains excellent, larger water intakes can be handled with relative ease without danger of either excessive retention of water or washing out of solutes. Such fluid must be very hypotonic, or even free from salts, since the ability to concentrate these solutes is diminished. A decreased fluid intake or an excessive amount of solutes demanding excretion may lead to dehydration, hyperosmolarity, disturbances of the central nervous system, and fever. A high serum sodium concentration is the laboratory clue to the cause of these symptoms. The reverse situation of excess water administration and insufficient solute load will likewise lead to temperature disturbances and central nervous system manifestations. Chemical determinations will assist in preventing these complications, but an even simpler method is to follow the infant's weight carefully. When a child is fed parenterally, particularly following surgery, one expects some weight loss unless there is local accumulation of fluids at the operative site. Failure to find a slow decline in weight is a danger signal that merits intensive investigation.

It might be well to point out here that values during growth may not be comparable to adult standards. For example, FIGURE 2 shows the normal blood findings during childhood. One is often tempted to transfuse a small child in order to increase the blood hemoglobin concentration to the adult normal standard of 15 gm. per cent. This may, however, be a polycythemic value for the 3-month-old child, whose normal hemoglobin value is 11 gm. per cent. The child would therefore be unnecessarily exposed to the risks of transfusion reactions, production of harmful antibodies, and even serum hepatitis. Incidentally, much of the anemia in infancy is nutritional in origin and should not be treated with transfusions for an elective operation. The hemoglobin concentration in nutritional iron deficiency will rise by as much as 0.3 gm. per cent of hemoglobin per day if treated with adequate amounts of iron and ascorbic acid orally. It is better to treat the infant for a week or two on such a regimen than to transfuse—a procedure that probably is more dangerous than many operations.

In premature and newborn infants the problems mentioned previously

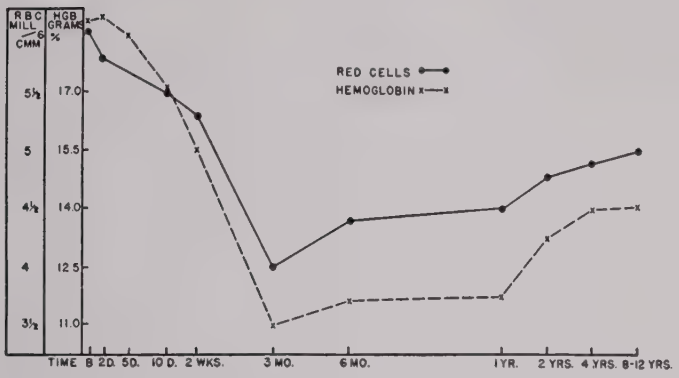

FIGURE 2. Normal blood values in infants and children (from Nelson[10]).

are greatly intensified. In addition, there is at birth an excessive water content, which is lost during the first week. This period is one of negative balances throughout, since the infant is normally not taking sufficient milk until the end of the first week. Attempts to treat these negative balances on a strictly chemical basis are not warranted and may cause difficulty, since the corrected state is not normal for the infant.

Strangely, the ability to withstand operation is surprisingly great during the first few days of an infant's life. This resistance then drops rapidly, to reach a minimum at approximately 3 months of age; then it rises rapidly through childhood. The actual basis for these changes in resistance to operative stress is not known, although they may be related to alterations in the adrenal cortex in the first few days of life. It is interesting that the changes in resistance to stress are roughly paralleled by the changes taking place in the immunity to many diseases. The child is born with antibodies derived passively from the mother. These diminish rapidly and the child's own antibody production begins to take over after several months. These time relations are important to remember in surgical care.

Part of the peculiar resistance to stress in very early life may be due to the type of defense that Smith[11] has termed passive or plastic resistance. The normal adult reacts violently to any stress and tends to bring his homeostatic mechanisms into play immediately so that very little change is permitted. Changes in his internal environment are tolerated poorly, and death may result from the extreme activity of his defense mechanisms. In contrast, the newborn, particularly the premature, infant is more pliant in his defense. Stresses tend to alter his internal environment to a greater degree before calling forth the much more feeble homeostatic mechanisms. He is more pliant and yielding whereas the adult is brittle. This type of defense can be extremely effective but, if the stress is prolonged, the relatively unresisting premature or newborn infant may be pushed into disaster without showing much sign of reaction. An example of this is the fact

that if water is withheld from the premature or newborn infant, the urine may eventually reach a respectable degree of concentration, but it may be found that the plasma sodium has risen to 170 mEq. per liter; the stress of dehydration has been met at the sacrifice of the exact maintenance of the internal environment. Such yielding tends to obscure clinical manifestations, so that the premature and newborn infant must be watched with extreme care. Even serious infections such as meningitis may be manifested by only very minor physical and clinical signs. Similar considerations apply to fluid and electrolyte therapy in the premature and newborn child. Since major difficulties may be present and show only minimal signs, a careful preoperative evaluation and proper correction of abnormalities is mandatory. Following surgery, these infants should be watched most carefully.

I have not discussed in detail the usual metabolic responses to surgery, such as elevated temperature, elevated pulse, decreased urinary volume, increased urinary nitrogen, increased urinary and plasma potassium, decreased excretion of sodium, and decreased tolerance for both sodium and pure water. In the infant and child these responses are similar to those in the adult, and they require similar precautions, such as minimizing the sodium intake during the first 3 days after operation, avoidance of potassium-containing solutions during surgery unless there are marked deficits or losses in potassium, and maintenance of a careful watch on weight, water intake, and urinary output.

Before closing, I should like to emphasize once more that most children need no special preoperative or postoperative parenteral fluid therapy. The parenteral administration of fluid can be avoided if the oral intake of liquids is maintained up to 4 or 5 hours preceding operation. Orders should be left to offer clear fluids to the child at specified intervals and at definite times rather than the usual prohibition, "No fluids after midnight." The child should be awakened in order to maintain his preoperative fluid and carbohydrate intake as long as possible. Following the operation, he should be offered fluids that he likes by a familiar individual—preferably his mother; generally, he will tolerate them well. In so far as parenteral therapy is concerned, initial corrections of those difficulties that threaten life should be made quickly, and further therapy should be undertaken gradually. For example, in threatened dehydration, acidosis or hypopotassemia, the "edge" should be taken off rapidly, but thereafter corrections back to normal should be made slowly, allowing the child's own homeostatic mechanisms to make the final correction. Otherwise the very sudden change and the possibility of overcorrection may do harm. We have all seen this in the formerly popular treatment of diarrheal acidosis by the administration of large amounts of alkali and salts. Edema, alkalosis, tetany, and other iatrogenic difficulties were thus produced as a result of our presumptuous belief that we could treat the infant or child as a chemical reaction without regard to his own homeostatic mechanisms or clinical state. Frequently we hasten to treat a single obvious abnormality, only to upset the infant's total adjustment to his illness. Another example of this is the

precipitation of tetany in an infant consequent to treatment of his acidosis according to well-known rules. Too much attention to minute details of chemical determinations may divert our attention from the fundamental clinical appraisal of the entire child and from his physiological state, reaction, and course.

Clement Smith[11] stated once that a physician should ask himself certain questions when approaching an infant. I should like to conclude by repeating these questions: "Is the behavior that the child presents acceptable and within normal limits for him? Am I certain that I can correct it better than can the infant if he is left to himself?"

References

1. Gross, R. E. 1953. The Surgery of Infancy and Childhood. W. B. Saunders. Philadelphia, Pa. & London, England.
2. Lowe, C. U. 1955. Practical thoughts on electrolyte and fluid administration. Pediatrics. **15**: 498.
3. Pickering, D. E. & R. W. Winters. 1954. Fluid and electrolyte management in children. Pediatric Clin. N. Amer. **1**: 873.
4. Thompson, D'Arcy W. 1942. On Growth and Form. Macmillan. New York, N. Y.
5. Talbot, N. B., G. A. Kerrigan, J. D. Crawford, W. Cochran & M. Terry. Application of homeostatic principles to the practice of parenteral fluid therapy. New Engl. J. Med. **252**: 856, 898.
6. Darrow, D. C. 1948. Disturbances in electrolyte metabolism in man and their management. Bull. N. Y. Acad. Med. **24**: 146.
7. Talbot, N. B., E. H. Sobel, J. W. McArthur & J. D. Crawford. 1952. Functional Endocrinology. Harvard Univ. Press. Cambridge, Mass.
8. Smith, H. W. 1951. The Kidney. Oxford Univ. Press. New York, N. Y.
9. Barnett, H. L. & J. Vesterdal. 1953. The physiologic and clinical significance of immaturity of kidney function in young infants. J. Pediatrics. **42**: 99.
10. Nelson, W. E. 1954. Textbooks of Pediatrics. 6th ed. W. B. Saunders. Philadelphia, Pa. & London, England.
11. Smith, C. A. 1956. The newborn patient. Pediatrics. **16**: 254.

CONTRIBUTION OF RADIOACTIVE ISOTOPES TO THE STUDY OF ELECTROLYTE BALANCE IN SURGERY

By Betty M. Cooper

Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn., under contract with the United States Atomic Energy Commission

Although chemical studies of blood in surgical patients may reveal changes in electrolyte concentrations, the extent of the changes in the body as a whole may not be apparent. Depletion or accumulation of electrolytes, increase or decrease of body water, and changes in fluid compartments may occur slowly and become extensive without producing changes apparent on physical examination or on chemical examination of the blood. This is particularly true in patients with cancer and other chronic diseases. Moore[1] has demonstrated marked changes in body water in patients with cancer, thermal burns, thyrotoxicosis, infection, and intestinal obstruction. Aikawa[2] has shown a significantly low exchangeable potassium content in uncontrolled diabetics. In his patients, blood plasma concentration was normal. If a patient who is to undergo surgery has suffered a loss of electrolyte or of body fluid, he has only a small reserve with which to compensate for further losses. On the other hand, a patient possessing an expanded fluid space may suffer great embarrassment from fluid given during surgery. With the use of radioactive tracer studies, such abnormalities can be revealed and corrected before surgery.

We are fortunate in possessing radioactive isotopes of metabolically essential elements having physical characteristics suitable for tracer studies in human beings.

The study of total body composition with radioactive isotopes is an application of the principle of dilution. This principle was first applied in medical studies undertaken by Keith, Rowntree, and Geraghty[3] in their early work on blood volume. The method has been refined and extended and is now used widely in physiological studies. A dilution study falls into one of three types. By dissolving a solid in a liquid, the volume of the liquid may be determined from the resulting concentration of the solid. By adding a measured amount of liquid to an unknown volume of liquid, the volume of the unknown can be determined. The mixing of a solid in a solid similarly allows determination of the weight of the unknown solid. The antipyrine method of determining body water is an example of the first type. The use of heavy water to determine body water is an example of the second technique, and the use of radioactive sodium and potassium to determine the total exchangeable element is an example of the third procedure.

To be satisfactory for use in dilution studies in medicine, a radioactive isotope must mix and equilibrate with its stable isotope without isotope effect; that is, the body must not be able to distinguish the radioactive isotope from the stable element. Metabolism of the material must not be

rapid, and it must be possible to secure equilibrium samples for assay. The results of studies with radioactive isotopes must be reproducible.

The calculations of all isotope dilution measurements are based upon the solution of a simple formula

$$V_2 = \frac{C_1 V_1}{C_2}$$

where C_1 = the concentration of the tracer material introduced; V_1 = the volume of the tracer material introduced; C_2 = the concentration of the tracer material after dilution equilibrium; and V_2 = the volume in which tracer material equilibrated. In radioactive isotope studies, $C_1 V_1$ is the total radioactivity injected and C_2 is the activity per unit after dilution. When this principle is applied to the measurement of the weight of an element, C_2 is expressed as activity per gram of stable element and is called "specific activity." Then V_2 gives the total weight of the stable element. If, during the equilibration of the radioactive isotope with the body content of the stable element, there is loss of isotope through excretion, this loss must be measured, and the total activity injected must be corrected for the loss.

When a radioactive isotope is injected into the blood, frequent blood sampling will show changing levels of activity until equilibration is completed. During mixing of the isotope the activity rapidly rises to a peak, then declines until mixing is complete. When activity is plotted against time, the curves obtained for all isotopes will have similar configurations, but will differ in activity-time relationships depending upon the extent and rapidity of mixing and equilibration and upon the site of the sampling.

Total Body Water

Total body water may be measured by the dilution of deuterium (H^2), the heavy stable isotope of hydrogen, or by tritium (H^3), the radioactive isotope. Tritium has a half life of 25 years and a very low-energy β radiation of 0.02 Mev. Deuterium is administered as deuterium oxide (heavy water). Equilibrium distribution occurs in 2 hours. Deuterium is analyzed either by the falling-drop density measurement or by the mass spectrometer. Tritium is administered as labeled water. Equilibrium distribution with tritium also occurs in 2 hours. FIGURE 1 is a typical equilibration curve for tritium. The disappearance curve for H^3 is used to determine the rate of water metabolism or turnover and is a measure of metabolic rate. Normal half time is 9 to 11 days. Radioactivity is measured in an ionization chamber. Total body water measured with these isotope methods shows good agreement, but the volume determined is a little larger than that obtained from measurements made with antipyrine. It is thought that this discrepancy occurs because tritium and deuterium exchange with the exchangeable hydrogen of organic compounds, but the exchange is small in comparison with the volume of body water.

Body water is distributed throughout all the tissues except fat. The

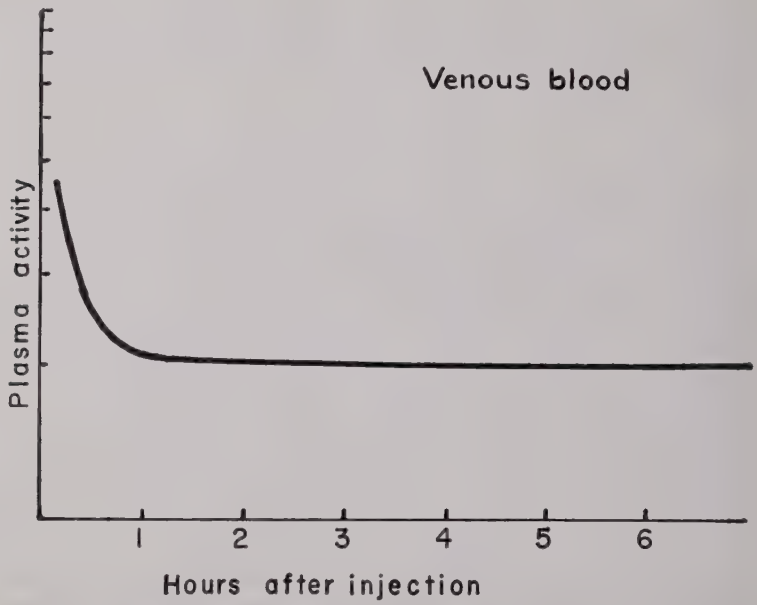

FIGURE 1. A typical equilibration curve following intravenous injection of tritium-labeled water.

chief variable in the relation of body water to weight is the fat content of the body. The water content of lean tissue of the body (75 per cent) is remarkably constant during health. If the volume of body water is known, Pace's[4] formula gives the fat content of the body.

$$\text{Percentage fat} = 100 - \frac{\%\ \text{water}}{0.732}$$

The proportion of body water to body weight varies throughout the life span. Body water is a linear function of weight in babies and children. In adults, women have a lower body-water to body-weight ratio than men because of the development of a greater amount of fat. With advancing age the ratio decreases further. As Moore[5] has said, babies are very juicy and elderly people are very dry. In men the total body water is 61 per cent of body weight and in women 52 per cent. In pathological states when the lean body mass is not constant, determinations of body water are of limited value without a quantitative method for measuring fat.

Fallot and Aeberhardt[6] have given tritium-labeled water orally and followed the level of activity in the blood. Water is absorbed rapidly and tritium activity appears in the blood shortly after oral administration. They analyzed the absorption curves for the rates of absorption and equilibration and determined the volume of total body water. They suggested the use of this technique in postoperative patients to determine when the patient is

ready for oral feeding and to facilitate proper hydration of patients on parenteral maintenance.

In a study of normal pregnant women, Haley and Woodbury[7] found that there was a retention of water at the end of pregnancy. In the immediate postpartum period there was an increase in the water turnover rate that returned to normal by the fourth day. During the first postpartum week there was a loss of body solids and, in most patients, there was a net loss of body water.

Electrolyte Studies

Sodium and potassium are two important electrolytes that can be studied with radioactive isotopes. Sodium-24 has a physical half life of 14.8 hours and decays by β and γ radiation. Potassium-42 has a half life of 14.4 hours and also decays by β and γ radiation. The half life and the radiation characteristics of Na^{24} and K^{42} are so similar that, when these isotopes are used together, they must be separated by chemical methods to measure the specific activity of each.

Total exchangeable sodium. When Na^{24} is injected intravenously there is a rapid rise and fall of activity during the mixing; the curve flattens in 40 to 60 minutes. Between 1 and 4 hours there is a gradual decrease in activity and after 4 hours there is a more gradual fall for many hours (FIGURE 2). The first equilibrium phase represents the penetration of

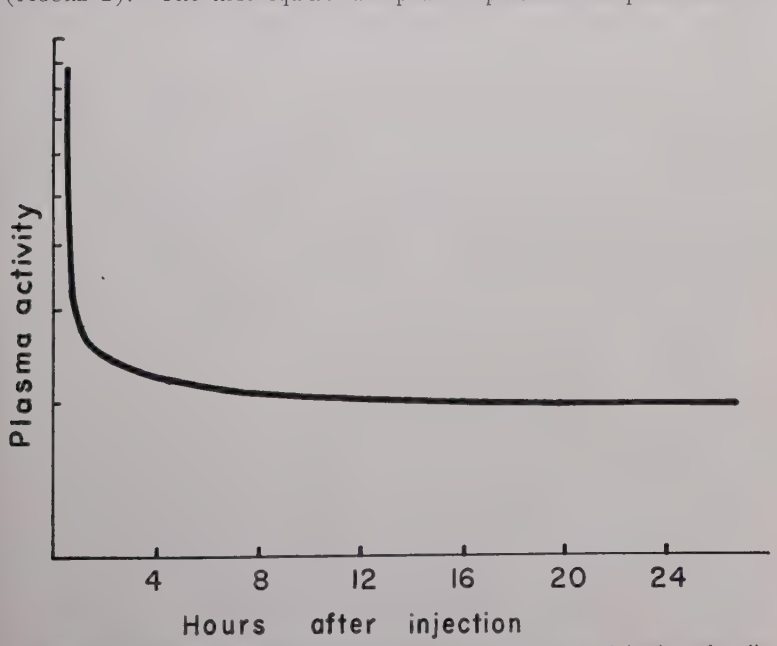

FIGURE 2. A typical equilibration curve following intravenous injection of radioactive sodium.

sodium into the extracellular space. A calculation from the blood activity at this time gives the volume of the "sodium space" or extracellular fluid volume. This volume may be larger than the extracellular fluid volume determined by other methods, for example, by the sucrose method.

Sodium is largely extracellular and potassium is intracellular. In order to interpret results of studies with Na^{24} it is necessary to distinguish total body sodium from total exchangeable sodium (Na_e). Although a large part of the exchangeable sodium is in the extracellular fluid, a small amount is intracellular, and a sizable amount is present in bone. Of the bone sodium, about 40 to 60 per cent is exchangeable in 24 hours. Using Na^{22}, which has a long half life, Moore[5] observed the sodium activity of bone over several months and found that the level of exchange varied little after 24 hours. The exchangeable bone sodium is of importance because it is measured as a part of the total exchangeable sodium and because it is probably physiologically active. Sodium-24 enters ascitic fluid promptly and equilibrates with it in a few hours.[8]

The value for total exchangeable sodium is variable in normal individuals, with a range of 29 to 46 mEq./kg. body weight and a mean value of about 41 mEq./kg. body weight in men and 39 mEq./kg. in women.

Total exchangeable potassium. Whereas determination of exchangeable sodium does not measure the total body sodium, the determination of exchangeable potassium (K_e) measures about 95 per cent of total body potassium.

After intravenous injection of K^{42}, equilibrium is attained within 24 hours in all parts tested except red blood cells and brain, in which the total content is only about 2 per cent of the total body potassium. Urinary excretion of potassium reaches equilibrium between 20 and 40 hours. Total exchangeable potassium may be calculated from the specific activity of either blood or urine after equilibrium is established. FIGURE 3 is a typical blood equilibration curve for K^{42}. The values for exchangeable potassium show a variation from 30 mEq./kg. to 58 mEq./kg. body weight. The mean K_e in normal men is about 47 mEq./kg. body weight. A greater variation in the mean value has been reported for women; Edelman[9] and Moore[5] found 41 mEq./kg. body weight. Aikawa[10] found the mean value for women to be 31.5 mEq./kg. body weight. This variation may be due to a difference in the population sampled.

Most patients in the postoperative period will show some decrease in exchangeable potassium; this is rapidly corrected when the patient resumes a normal diet. In many conditions, such as starvation, cirrhosis, poorly controlled diabetes, severe renal insufficiency, intractable asthema, Addison's disease, and intestinal obstruction with vomiting, the exchangeable potassium may be reduced to as much as 50 per cent of normal. The serum potassium in many of these patients may be normal.

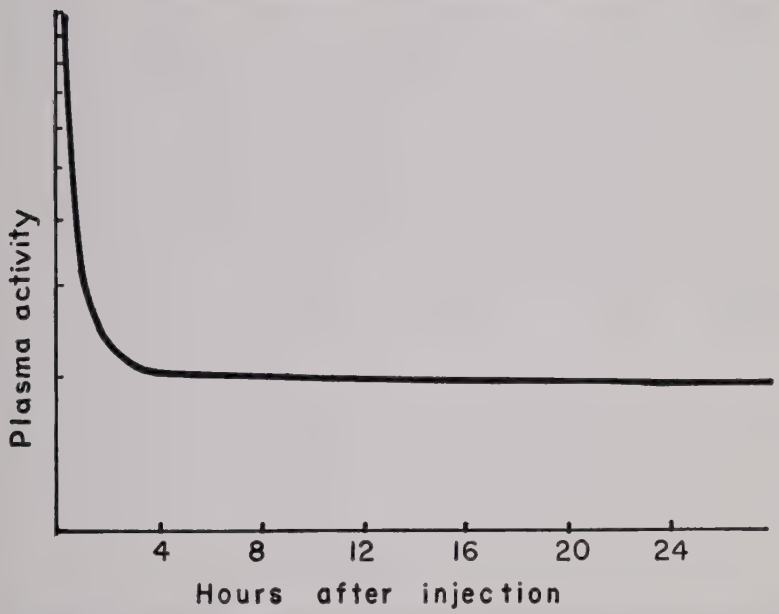

FIGURE 3. A typical equilibration curve following intravenous injection of radioactive potassium.

Conclusion

The radioactive materials provide excellent tools for the study of total body composition in surgical patients. There are limitations to their usefulness, and these are unfortunately most apparent in the disease states in which we are most anxious for definite information. However, when we learn to apply these tools more widely, we shall have attained a more thorough understanding of the changes that occur in the preoperative and postoperative periods.

References

1. MOORE, F. D., H. B. HALEY, E. A. BERING, JR., L. BROOKS & I. S. EDELMAN. 1952. Further observations on total body water. II. Changes of body composition in disease. Surg. Gynecol. Obstet. **95**: 155.
2. AIKAWA, J. K., J. H. FELTS, JR. & G. T. HARRELL, JR. 1953. Isotopic studies of potassium metabolism in diabetes. J. Clin. Invest. **32**: 15.
3. KEITH, N. M., L. G. ROWNTREE & J. T. GERAGHTY. 1915. Method for determination of plasma and blood volume. Arch. Intern. Med. **16**: 547.
4. PACE, N. & E. N. RATHBUN. 1945. Studies of body composition. III. The body water and chemically combined nitrogen content in relation to fat content. J. Biol. Chem. **158**: 685.
5. MOORE, F. D. 1955. Body composition. An introduction to the clinical and investigative use of isotope dilution methods. *In* Radioisotopes in Medicine. G. A. Andrews, M. Brucer & E. B. Anderson, Eds. ORO-125. U. S. Govt. Printing Office. Washington, D. C.

6. Fallot, P. & A. Aeberhardt. 1956. Use of tritium-containing water as an indicator of water metabolism in normal and postoperative subjects. *In* Peaceful Uses of Atomic Energy: Proceedings of the International Conference in Geneva, August 1955. **10.** Radioactive Isotopes and Nuclear Radiations in Medicine. United Nations. New York, N. Y.
7. Haley, H. B. & J. W. Woodbury. 1952. Observations on body composition and body water metabolism in normal pregnancy. J. Clin. Invest. **31:** 635.
8. Farr, L. E. 1955. The use of radioactive isotopes in a study of extracellular space. *In* Radioisotopes in Medicine. G. A. Andrews, M. Brucer & E. B. Anderson, Eds. ORO-125. U. S. Govt. Printing Office. Washington, D. C.
9. Edelman, I. S., J. M. Olney, A. H. James, L. Brooks & F. D. Moore. 1952. Body composition: Studies in the human being by dilution principle. Science. **115:** 447.
10. Aikawa, J. K., G. T. Harrell, Jr. & B. Eisenberg. 1952. The exchangeable potassium content of normal women. J. Clin. Invest. **31:** 267.

Part IV. Hypotension in the Operating Room

RELATIONSHIP OF ANESTHETIC AGENTS TO HYPOTENSION

By Robert T. Patrick

*Section of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minn.**

Interest on the part of anesthetists in the relationship of anesthetic agents to hypotension prompts the question of why anesthetists are at all concerned with blood pressure. The answer is that to a certain extent its measurement provides a means by which circulatory efficiency may be estimated. Probing deeper, one comes to the realization that the real interest of anesthetists in blood pressure is in the ability of the circulatory system to provide each organ with a flow of blood adequate to support the needs of that organ. Resistance to flow is offered by the tubular ramifications that compose a portion of the circulatory system. The blood pressure is the force tending to drive a volume of fluid across a vascular bed. The relationship between the factors I have mentioned can be expressed in a highly simplified equation:

$$\text{Mean blood pressure} = \text{cardiac output} \times \text{peripheral resistance}$$

Of the three, only blood pressure can be measured rapidly and simply. Cardiac output can be determined only by techniques unsuitable for application in everyday practice. Peripheral resistance cannot be measured at all, but can be calculated from observations on blood pressure and cardiac output.

In this relationship, mean blood pressure plays a passive part inasmuch as it is a resultant of the other factors: the cardiac output and the degree of peripheral resistance. Cardiac output and peripheral resistance, although influenced indirectly by pressure, may be regarded as fundamental and independent functions, but they are responsive to factors other than those expressed in the equation. Cardiac output depends primarily on venous return and manifests itself in varying products of stroke volume and heart rate. Peripheral resistance depends on the tubular length and cross-sectional area of the precapillary system and on the viscosity of the blood.

The ministrations of the anesthetist can alter any of these variables individually or collectively. Should the total peripheral resistance decrease, cardiac output must increase if pressure is to be maintained. Should cardiac output decrease, the total peripheral resistance must increase to maintain pressure. However, if cardiac output decreases and if peripheral resistance increases equally in every vascular bed to a degree sufficient to maintain pressure, each vascular area is deprived of a flow of blood proportionate to the decrease in output in spite of maintenance of blood pres-

* The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

sure. Certain tissues, such as skin and muscle, under resting conditions can tolerate a pronounced reduction in blood flow. Other tissues, notably heart and brain, even under resting conditions have basic requirements for blood flow that must be met. If cardiac output decreases and peripheral resistance in such vascular regions as skin and muscle increases, then the blood flow to tissues, the needs of which are critical, can be maintained. Herein lies the implicit value to anesthetists of estimating blood pressure. When the blood pressure is maintained the anesthetist assumes that, regardless of variations in total blood flow or in total peripheral resistance, regional adjustments in flow and resistance are taking place to meet the needs of the tissues that have the greatest requirements.

We must accept the fact that most anesthetic agents now in common use cause a decrease in cardiac output, although present knowledge does not tell us whether this is due to a decreased demand by the organism or a toxic effect of the agents. The degree of interference imposed by these agents on mechanisms for controlling peripheral vascular reactivity then assumes great importance, for it is only by reduction of blood flow to certain regions that essential flow is maintained to the other areas.

Brewster and his co-workers[1] demonstrated that during ether anesthesia the cardiac output of sympathectomized and adrenalectomized dogs decreases. Brewster proposed that during ether anesthesia a release of epinephrine and norepinephrine tends to maintain or increase cardiac output and peripheral resistance. In a study of the response of human beings to ether anesthesia Fletcher and his associates[2] related the observed increases in cardiac output to excitement during induction. Patients who did not experience such excitement were found to have decreased cardiac output. Data from these observations are plotted in FIGURE 1. With a few exceptions, decrease in cardiac output was accompanied by increase in peripheral resistance to a degree sufficient to maintain mean blood pressure near the preanesthetic level.

Etsten,[3] Fieldman,[4] and their colleagues observed a consistent decrease in cardiac output in patients undergoing anesthesia with thiopental sodium, nitrous oxide, and oxygen. They demonstrated that the degree of decrease in cardiac output is greater as the depth of anesthesia increases and that, as anesthesia is permitted to lighten, there is a slow return toward initial values. Data from Fieldman's observations are shown in FIGURE 2. In a number of instances these data appear to indicate interference with peripheral vascular activity during anesthesia, although in other instances rather large decreases in cardiac output are compensated by pronounced increases in peripheral resistance.

Etsten,[5] Thompson,[6] and their associates demonstrated an almost invariable decrease in cardiac output during anesthesia with cyclopropane and oxygen in man. Thompson and his co-workers were able to demonstrate a close correlation between the degree of decrease and the depth of anesthesia; that is, decrease in cardiac output is greater during more profound anesthesia. With emergence of the patient to lighter planes of anesthesia,

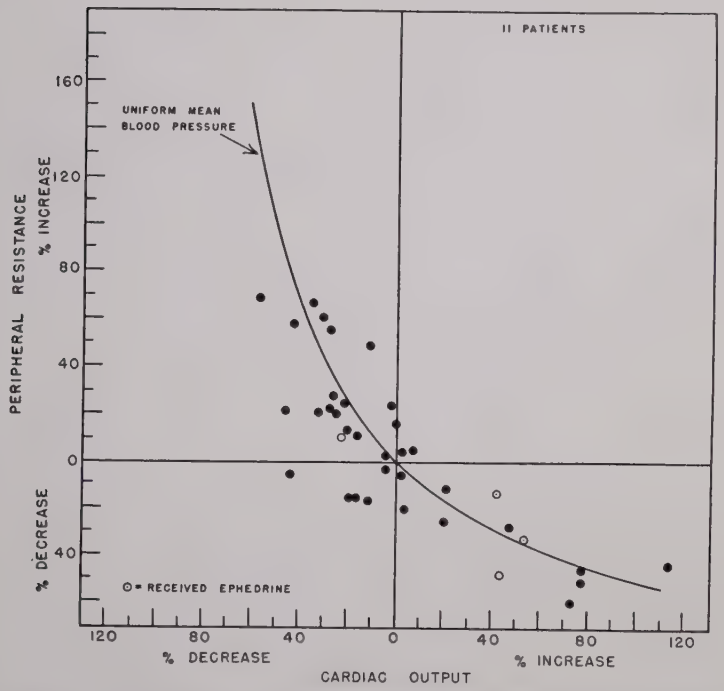

FIGURE 1. Data selected from observations made by Fletcher and his associates[2] on hemodynamics during ether anesthesia in 11 patients. The initial observation of cardiac output and peripheral resistance in each conscious patient lies at the intersection of the zero vertical line and the zero horizontal line. Decreases in cardiac output in percentage of the initial observations are plotted to the left of the vertical line and increases to the right. Increases and decreases in peripheral resistance are plotted above and below the horizontal line, respectively. Variations in percentage of cardiac output and of peripheral resistance just sufficient to maintain a uniform mean arterial blood pressure fall on the curved line. Decreases and increases in mean arterial blood pressure lie to the left and right of the curved line, respectively.

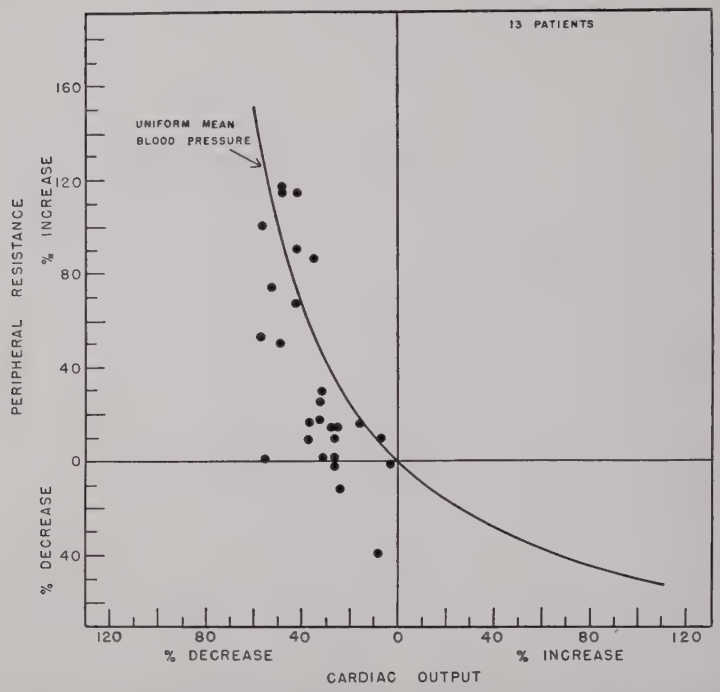

FIGURE 2. Data selected from observations made by Fieldman and his associates[4] on hemodynamics during anesthesia with thiopental sodium and nitrous oxide in 13 patients.

values for cardiac output return rapidly toward the initial observations. Data are shown in FIGURE 3. Under these conditions there appears to be some overactivity of the mechanisms responsible for maintaining or increasing peripheral resistance.

Summary

Estimation of blood pressure is essential in that it is one of the few useful measurements of circulatory efficiency readily available. It is useful only if it is interpreted correctly as a number that is a resultant of two factors, cardiac output and peripheral resistance, that are themselves subject to many influences. Of these two factors, cardiac output supplies the needs of the whole organism, and peripheral resistance influences the proportion of cardiac output delivered to the regions that have the greatest need at the time. Decrease in cardiac output appears to be an inevitable accompaniment of anesthesia with the agents now in use. Present knowledge does not tell us whether this reflects decreased demands of the organism or toxic effects of the agents themselves. In the absence of such knowledge, consideration of peripheral vascular activity during anesthesia

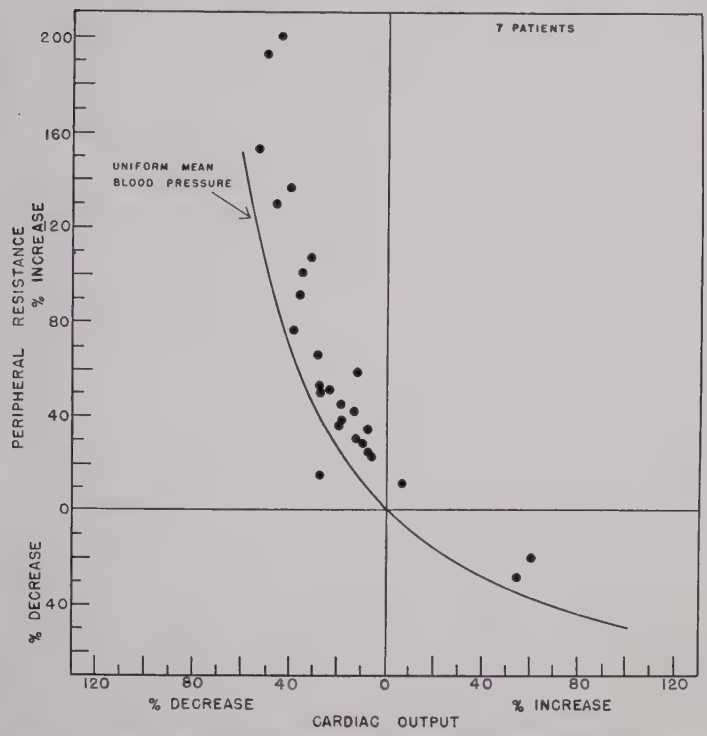

FIGURE 3. Data selected from observations made by Thompson and his associates[6] on hemodynamics during anesthesia with cyclopropane in seven patients.

is important. The relationships between observations of pressure, cardiac output, and peripheral resistance during anesthesia with thiopental sodium and nitrous oxide, with ether, and with cyclopropane are presented.

References

1. BREWSTER, W. R., JR., J. P. ISAACS & T. WAINØ-ANDERSEN. 1953. Depressant effect of ether on myocardium of the dog and its modification by reflex release of epinephrine and nor-epinephrine. Am. J. Physiol. **175:** 399.
2. FLETCHER, G., J. W. PENDER & E. H. WOOD. 1956. Hemodynamic effects of ether anesthesia and surgery in 11 cases. Current Researches Anesthesia & Analgesia. **35:** 18.
3. ETSTEN, B. & T. H. LI. 1955. Hemodynamic changes during thiopental anesthesia in humans: Cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume. J. Clin. Invest. **34:** 500.
4. FIELDMAN, E. J., R. W. RIDLEY & E. H. WOOD. 1955. Hemodynamic studies during thiopental sodium and nitrous oxide anesthesia in humans. Anesthesiology. **16:** 473.
5. ETSTEN, B. E., H. F. RHEINLANDER, R. N. REYNOLDS & T. H. LI. 1954. Cardiac output and related hemodynamics during cyclopropane anesthesia in humans. Federation Proc. **13:** 352.
6. THOMPSON, M. C., R. T. PATRICK & E. H. WOOD. Unpublished data.

ADRENOCORTICAL INSUFFICIENCY DURING SURGICAL ANESTHESIA

By Charles L. Burstein

Department of Anesthesiology, The Hospital for Special Surgery, New York, N. Y.

Considerable interest in adrenocortical function during and following surgical intervention has been aroused in recent years. Two types of deficiency should be considered in relation to the generally accepted concept that stress caused by surgical trauma results in pituitary-adrenocortical stimulation: one is adrenal insufficiency due to excessive surgical trauma; the second is the development of adrenocortical insufficiency following even relatively mild surgical trauma because of impaired adrenal function in patients previously treated with cortisone or similar adrenocortical steroids.

The adrenal cortices of a patient become deficient after treatment for more than 2 weeks with adrenal steroids. If therapy is withdrawn abruptly the patient reacts as would a subject with Addison's disease. If corticosteroid therapy, usually taken orally, is discontinued the night before an operation, the superimposed surgical trauma may precipitate an acute adrenal insufficiency, manifested by metabolic imbalance and arterial hypotension.[1–4]

Anesthesia *per se* may not actually aggravate such conditions. However, the anesthesiologist, as well as other members of the surgical team, is confronted with certain relevant problems that bear upon the diagnosis and treatment of adrenocortical insufficiency during surgery or immediately thereafter.

Arterial hypotension is one of the signs of acute adrenal insufficiency, but it is usually a late manifestation. During surgical intervention, it is important to distinguish this type of hypotension from the reflex hypotension incident to mechanical stimulation of autonomic areas possessing vagal cardiac effector pathways, or from hypotension due to hypovolemia as a result of hemorrhage.

In this presentation, the following points will be considered: (1) basic concepts of adrenocortical function; (2) the modifying role of anesthesia; (3) behavior during relatively minor surgical operations of patients with adrenocortical insufficiency who are not receiving adrenocortical steroid therapy; (4) behavior during major surgical interventions of patients with adrenocortical insufficiency supported by adequate hormonal therapy; (5) behavior of patients during major surgery resulting in adrenocortical insufficiency.

Basic Concepts of Adrenocortical Function

The adrenal cortex secretes a number of steroids, which have various functions, including homeostatic regulation of the volume and composition

of body fluids. About 40 adrenal steroids have been isolated and have been divided into 3 groups of compounds. These include:

(1) Glucocorticoids, such as cortisone and hydrocortisone, which affect predominantly carbohydrate and protein metabolism. They produce regression of lymphoid tissue and have an antihyaluronidase effect, resulting in decreased cell permeability. They also cause salt retention and potassium loss, but to a lesser degree than the mineralocorticoids.

(2) Mineralocorticoids, such as desoxycorticosterone (DCA). These steroids produce predominantly sodium retention and potassium loss.

(3) Androgenic steroids. These substances are concerned in the production of secondary sex characteristics and exert a protein-sparing effect.

In the normal subject there is a chain of reactions that maintains an adequate secretion of the adrenal steroids. The adrenocorticotropic hormone (ACTH), secreted by the anterior pituitary, acts upon the adrenal cortex, causing secretion of the adrenocortical steroids. Various conditions of "stress," such as tissue trauma, cause increased anterior pituitary activity and therefore augmented secretion of ACTH, which, in turn, stimulates the secretion by the adrenal cortex of steroids that are utilized at the site of trauma.[5] Depletion of adrenocortical compounds from the blood also is able to stimulate the adenohypophysis to secrete ACTH.[6] Interrelated in this pituitary-adrenocortical axis is the functioning of the hypothalamus, stimulation of which causes pituitary stimulation and ACTH release, whereas depression of the hypothalamus causes depression of the anterior pituitary and diminished ACTH secretion.[7, 8] The hypothalamus-pituitary-adrenocortical system can also be activated from the site of the stress via the sympathetic fibers to the adrenal medulla, resulting in epinephrine release. The increased concentrations of epinephrine that reach the hypothalamus by way of the systemic circulation also result in the release from the hypothalamus of a humoral substance that stimulates the anterior pituitary to secrete more ACTH, which again activates the adrenal cortex.[9]

Following trauma in subjects with intact adrenals, as was observed in soldiers wounded in battle in Korea in 1952,[10] the adrenocortical response is characterized for at least 24 hours after trauma by: (1) increased concentration of the 17-hydroxycorticosteroids in the blood plasma; (2) increased urinary excretion of the 17-hydroxycorticosteroids and of the acid-fraction steroids;[11] (3) a diminution by more than 50 per cent of the circulating eosinophils in the blood; (4) a significant retention of sodium due to diminished urinary excretion of sodium; and (5) increased urinary excretion of potassium. When the adrenals are sufficiently active, similar effects appear following surgical trauma.[12–15]

Similar effects are also produced in the Thorn ACTH test used in the diagnosis of adrenal function.[16] For this test, 25 U.S.P. units of ACTH in 500 cc. of physiological saline or 5 per cent dextrose in water are either injected intramuscularly[17] or, preferably, infused intravenously over an 8-hour period on each of 2 successive days, starting at 9 a.m. without subjecting the subject to fasting.[16]

In subjects with normally functioning adrenal glands, the administration of ACTH during conditions of surgical trauma when the level of the 17-hydroxycorticosteroids in the plasma has risen significantly will result in a further increase of the level of the 17-hydroxycorticosteroids.[13] This finding makes it clear that, during major surgical trauma, the adrenocortical glands are not maximally stimulated, since the exogenous administration of ACTH can still result in further secretion of the adrenal corticoids.

The main types of adrenal insufficiency are: (1) primary adrenocortical insufficiency (Addison's disease); (2) secondary adrenocortical insufficiency (hypopituitarism); (3) iatrogenic adrenocortical insufficiency (induced following medical treatment with corticosteroids); and (4) adrenocortical insufficiency due to extreme stress (with exhaustion of the adrenal cortices, as in severe shock). In any of these conditions, there is: (a) decreased concentration of the 17-hydroxycorticosteroids in the blood plasma; (b) decreased urinary excretion of the 17-hydroxycorticosteroids and of the acid-hydrolyzable steroid fraction; (c) little or no fall and, occasionally, a rise in the circulating blood eosinophils; (d) diminution of the plasma sodium concentration; accompanied by (e) marked loss of sodium chloride in the urine.

In these situations, the Thorn ACTH test shows a lack of response; there is no increase in the urinary excretion of the 17-hydroxycorticosteroids; and the eosinophils in the blood show no diminution in number.

These tests require several hours for determination and evaluation. An emergency may force the use of a more rapid test involving a determination of the concentration of sodium simultaneously in the blood plasma and in the urine.[18] For this, 5 cc. blood are taken from a vein and 5 cc. of urine are withdrawn from the bladder by means of a catheter. The sodium concentrations in the plasma and urine are then rapidly determined by a flame photometer. In adrenocortical insufficiency there is a significant reduction in the serum sodium concentration (less than 130 mEq. per liter) and a high excretion of sodium in the urine (more than 100 mEq. per liter).

The Modifying Role of Anesthesia in Adrenocortical Function

Anesthesia and depressant drugs—such a drug as morphine—may alter the activation of the hypothalamus-pituitary-adrenal system.

The establishment of anesthesia using cyclopropane, ether, or thiopental-nitrous oxide results in an increased concentration of the 17-hydroxycorticosteroids in the blood plasma.[13, 19] This increase is statistically significant; the average rise is from 13 μg. to 19 μg. per 100 cc.[13]

Changes in the circulating eosinophils, however, do not conform with the usual response to adrenocortical stimulation, which is characterized by eosinopenia. In determinations of the eosinophil counts in the blood of patients anesthetized with cyclopropane or with cyclopropane and ether for surgical procedures lasting 2 to 4 hours, it was found that only 3 of 23 patients manifested a decrease in the circulating eosinophils of more than

50 per cent during surgical anesthesia at a period 2 hours after the start of surgery. Since none of these patients showed any evidence of shock at this time, a definite eosinopenia would have been expected in all these cases. Determinations of eosinophil counts in the postoperative period, 5 hours after the start of surgical procedures, when the effects of anesthesia had become dissipated, then revealed the development of eosinopenia in 19 of the 23 patients.[20] It would seem, therefore, that general anesthesia modified the usual eosinopenic response to surgical trauma.

In 37 patients who were given spinal anesthesia without preanesthetic medication and without vasopressor or other drugs, and whose arterial blood-pressure levels remained within normal limits during the surgical interventions, the eosinopenic response to surgical trauma was modified also. When measurements were made 2 hours after the start of surgery, a diminution of 50 per cent or more of the circulating eosinophils was observed in only 13 of 37 patients. Three hours later, the same number of patients had an eosinopenic response. The changes in the eosinophil counts were almost the same in every instance at 2 hours and at 5 hours after the start of surgery.[20]

The simultaneous occurrence during general anesthesia of increased levels of 17-hydroxycorticosteroids in the plasma and normal values for the eosinophils is difficult to explain. The establishment of general anesthesia cannot be said to be a "stressful" state nor one causing trauma—particularly when an excitement stage is not produced following the administration of ultrarapid-acting anesthetic agents. There is the possibility that disturbances of liver function and of kidney function during general anesthesia may interfere with the usual conjugation and excretion of the adrenal corticosteroids,[21, 22] resulting in a disturbance of the balance between their secretion and their utilization, destruction, and excretion.[22]

Changes in kidney function have been shown to occur when the state of general anesthesia is produced by the administration of cyclopropane, ether, or thiopental sodium combined with nitrous oxide.[23] The altered effects, it has been observed, are characterized by an oliguria, with retention of sodium and of chloride. Studies of renal function during anesthesia have intimated that renal hemodynamic changes occur.[24, 25] These have been interpreted as being due to intrarenal vasoconstriction of both the afferent and the efferent arterioles, because of the concomitant reduction of 20 to 30 per cent in glomerular filtration and a reduction in renal plasma flow of 25 to 35 per cent. The 50-per cent decrease of urine flow during anesthesia is presumed to be due to a decrease in glomerular filtration and in renal plasma flow, as well as to increased reabsorption of water and electrolytes. It is difficult to determine whether these changes are due to increased adrenocortical secretion during general anesthesia or whether the rise in the corticosteroid level is due to their impaired excretion because of the changes in kidney function, or both.

Some drugs used for preanesthetic medication may modify adrenocortical activity. A recent report has shown that, in rats, the depressing effects of

morphine on the hypothalamus cause a diminution of secretion of ACTH by the pituitary that results in depressed adrenocortical function.[26] Previous experiments had demonstrated that the hypothalamus influences the secretion of ACTH by the pituitary; stimulation of selected hypothalamic centers was shown to provoke secretion of ACTH,[7, 27] whereas lesions in specific areas of the hypothalamus were observed to prevent the usual response of the pituitary to stimulation.[8] These reports therefore indicate that alterations in function of the hypothalamus, which often follow the administration of morphine or other depressant drugs, may diminish the secretion of ACTH from the pituitary, resulting in depression of adrenocortical activity.

A preliminary study of the effects of various preanesthetic medications in humans on the blood levels of the 17-hydroxycorticosteroids was reported recently.[19] It was found that the administration of therapeutic doses of pentobarbital (2 mg./kg.) produced a significant fall in the free serum corticoid level from 12 to 6 μg. However, since subsequent intravenous administration of ACTH resulted in the usual rise in the corticoids, it was inferred that pentobarbital probably interferes with the release or formation of ACTH, possibly by means of an altered hypothalamic threshold. The administration of morphine sulfate, in doses of 0.15 mg./kg., resulted in varied responses. Although the mean value dropped from 12 to 8 μg. it was concluded that the change was not statistically important since, of 13 patients studied, there was no change in 6, a slight rise in 3, and a fall in the corticosteroid level in 4. Atropine or scopolamine, in doses of 0.02 mg./kg., produced no change in the concentration of the corticosteroids.

Of great importance is the effect of psychic stress from apprehension and anxiety in the preoperative period. It has been reported that the urinary excretion of the 17-hydroxycorticosteroids in a group of 10 healthy subjects rose from a mean level of 1 to 4 μg. per minute, while they were tranquil, to 5.6 to 8.3 μg. per minute when feelings of apprehension, anger, or excitement were present.[28]

As to the over-all effect of anesthesia on adrenocortical function, it would seem that anesthesia tends to block the traumatic stimuli during surgical intervention since, when anesthesia is ended, the adrenocortical response then becomes fully manifest; the rise in the plasma level of the 17-hydroxycorticosteroids appears to be related to the extent and duration of the surgical trauma.[13] A number of clinical reports have shown that adrenocortical insufficiency due to surgical trauma can appear at the time when anesthesia is ended.[2, 3, 29]

Behavior of Patients with Adrenocortical Insufficiency During Relatively Minor Surgical Operations without Adrenocortical Steroid Therapy

The following case report is typical of the effects that may be produced following a relatively minor surgical intervention in a patient with iatro-

genic adrenocortical insufficiency whose corticosteroid therapy had been inadvertently discontinued.

Case 1. A man 61 years of age was brought to the hospital in acute distress on November 7, 1954. A diagnosis of appendicitis was made, and immediate surgical intervention was proposed. The patient's physical condition seemed good, although he appeared pale and his hemoglobin content in the blood was 11.4 gm. per 100 cc. Appendectomy and drainage of a retrocecal abscess were performed during cyclopropane anesthesia. Preoperatively, he was given an infusion of 1000 cc. 5 per cent dextrose in water. During the operation, intravenous therapy (250 cc. saline and 500 cc. of blood) was continued at the surgeon's request because the patient appeared pale and toxic. During the operation, the patient's arterial blood pressure, pulse rate, and respiratory rate remained normal. Immediately after the operation, as he was emerging from anesthesia, he became pale and cold, with excessive perspiration; his pulse became thready and rapid, at a rate of 140 per minute; and his arterial blood pressure fell to below 80 mm. Hg systolic. It was then disclosed that this patient had been receiving hydrocortisone therapy for rheumatoid arthritis for the past 3 years. As soon as this fact became known, an intravenous administration of 100 mg. of hydrocortisone (free alcohol) in 1000 cc. of 5 per cent dextrose in saline was begun. This therapy resulted in considerable improvement, with recovery to normal vital functions. Nine days later, the patient eviscerated. Closure was made with through-and-through silk sutures during cyclopropane anesthesia. At this time an intravenous infusion of 1000 cc. of 5 per cent dextrose in saline containing 100 mg. of hydrocortisone was administered. Postoperatively, he again manifested severe and immediate surgical shock and was then treated, with good results, by the intravenous administration of another 100 mg. of hydrocortisone. Four days later, he developed a fecal fistula. He died a week later following an episode of pyrexia that could not be aided by antibiotic therapy. Autopsy revealed massive septicemia, with abscesses scattered throughout the peritoneum, the peribronchial tissue, and the myocardium. The adrenals were atrophic: one adrenal gland weighed 3.2 gm., the other 5 gm., and they showed marked thinning of the cortex.

Similar mishaps have been reported by others.[1–3]

The case presented above illustrates that prolonged therapy with hydrocortisone can result in hypocorticism and that when such a patient requires surgical intervention, even of a minor nature, he may require supplemental hydrocortisone to treat a crisis of acute adrenocortical insufficiency. In this case, hypocorticism was demonstrated both anatomically and functionally. This case illustrates two other points that may be observed under similar conditions: first, that patients receiving corticosteroid therapy may develop a susceptibility to certain infections poorly responsive to antibiotics; second, that the administration of general anesthesia to such patients may block or delay the state of acute adrenal cortical insufficiency until the effects of anesthesia are dissipated.

Behavior of Patients with Adrenocortical Insufficiency During Major Surgical Interventions with Adequate Hormonal Therapy

In contrast to the previous case, the following report shows that, with proper adrenocortical therapy, patients with adrenal insufficiency can withstand major surgical interventions satisfactorily.

Case 2. A man 37 years of age, who had been known to have Addison's disease for 7 years, had been managed fairly successfully on a program in which desoxycorticosterone acetate pellets of 150 mg. were implanted every 3 months, and cortisone in doses of 25 mg. was taken daily orally. Due to a back injury, he had considerable pain that interfered with his daily routine. Orthopedic consultation suggested that he might be helped by a lumbosacral fusion together with a sacroiliac fusion. It was planned to manage this patient with hydrocortisone intravenously throughout the surgical period and postoperatively as needed, supplementing this with desoxycorticosterone acetate, saline, and cortisone as indicated.

The operation was accomplished on October 21, 1954. Preanesthetic medication consisted of Pantopon, 10 mg., and atropine sulfate, 0.4 mg., injected hypodermically 1 hour before induction of anesthesia. Anesthesia was produced by the intravenous injection of 300 mg. of Evipal Sodium in a 2 per cent aqueous solution, followed by the administration of cyclopropane with oxygen in a closed to-and-fro CO_2-absorption rebreathing technique. The endotracheal intubation was performed with a cuffed No. 36 Magill tube and the patient was turned into the prone position. The preanesthetic arterial blood pressure was 100 mm. Hg systolic and 64 diastolic. The pulse rate was 72 per minute. These circulatory levels were maintained remarkably stable throughout the entire operation, which lasted for over 3 hours. The electrocardioscope, which was observed during the procedure, showed a regular sinus rhythm at all times. Fluid therapy consisted of 2000 cc. of blood to compensate for a similar amount of blood loss produced by the lumbosacral fusion followed by the sacroiliac fusion. In addition, the patient received 100 mg. of hydrocortisone in 1000 cc. of 5 per cent dextrose in saline, administered intravenously during the surgical procedure.

The postoperative course was satisfactory in that no addisonian crisis developed at any time during the next 2 months. The urinary salt excretion during this time varied between 5 to 10 gm. a day and the arterial blood pressure was maintained within normal limits. To attain these effects, liberal amounts of desoxycorticosterone and saline were administered. Minor complications occurred: a mild urinary tract infection on the third postoperative day, a transfusion reaction characterized by mild angioneurotic edema, and a mild wound infection despite antibiotic therapy.

Behavior of Patients During Major Surgery Resulting in Adrenocortical Insufficiency

There presently exist divergent opinions concerning the development of adrenocortical insufficiency during traumatic surgery in patients with nor-

mal adrenals preoperatively. Certain observers contend that this complication is possible, and they cite examples of patients who manifested severe surgical shock that responded favorably to the administration of intravenous hydrocortisone.[30, 32] Others are skeptical of these claims and declare that the states of shock said to be due to adrenocortical insufficiency from exhaustion of the adrenal cortices were never proved by actual laboratory tests and that the improvement following intravenous hydrocortisone could have been due to other therapeutic measures that had been applied concomitantly.

One group of investigators[31] has presented a case of a patient who required revision of an esophagojejunostomy. During this procedure "multiple blood transfusions and both intravenous and intramuscular vasopressor agents were necessary to maintain blood pressure. After 8 hours, and in spite of the administration of 6 units of blood, these measures ceased to be effective and an infusion of hydrocortisone was started. For the remainder of the operation and the immediate postoperative period the blood pressure was successfully maintained." Examination of the operative chart presented for this case revealed the stated significant arterial hypotension during the surgical intervention. However, there was neither mention nor any record of the pulse rate. In an operative procedure, such as the one described, that requires continued manipulation about the esophagus, one can speculate whether the arterial hypotension could have been due to direct vagal stimulation; such stimulation would have been manifested by a bradycardia as well as by arterial hypotension. In that event, these circulatory disturbances would have been returned to normal merely by the cessation of the manipulation about the esophagus.

Another proponent of the adrenal exhaustion theory[30] cites the case of a 30-year-old woman who required a total hysterectomy for a ruptured uterus. Hemorrhage was severe, "estimated operative blood loss was 6000 cc.; replacement was 7000 cc. During operation, the generalized bleeding syndrome characteristic of an incompatible blood transfusion was noted, and whole fresh blood was begun. The hemorrhagic diathesis apparently was brought under control, but the patient's blood pressure remained at 80 mm. Hg systolic and 40 mm. Hg diastolic, irreversible to further transfusion. At this time the patient had received 8000 cc. of whole blood. The eosinophil count at this time was 89 cells per cubic millimeter, much higher than had been anticipated. A test dose of 50 cc. of aqueous adrenocortical extract was given, and the blood pressure immediately but transiently rose to 110 mm. Hg systolic. An immediate infusion was started consisting of 200 cc. of aqueous adrenocortical extract in 500 cc. of 5 per cent dextrose in distilled water. The blood pressure stabilized completely at 100 mm. Hg during and following the transfusions, and eosinophil counts were stationary, showing 0 cells per cubic millimeter. No shock state recurred during the remainder of the convalescence." Here again, although it was claimed that a test dose of adrenocortical extract resulted in a rise of the arterial blood pressure, it is possible that the inten-

sive blood transfusions might have been sufficient in themselves. As to the unexpectedly high eosinophil count of 89 cells per cubic millimeter during the operative procedure, there was no comparison available between this count and the preoperative eosinophil count, which might have been more than twice this amount. The value of 0 cells per cubic millimeter postoperatively was indicative of adrenal stimulation, but it was still possible that the relatively high count during surgical anesthesia could have been modified by the state of anesthesia alone.

Work is now in progress in many clinics, including our own, to determine by laboratory evidence whether traumatic surgical intervention can actually cause adrenocortical insufficiency in patients with previously normal adrenals. Conclusive data are not yet available. However, until definite evidence can be obtained, it is our opinion that whenever there develops a condition of shock that is not due to manipulative circulatory reflexes and that does not respond to adequate blood transfusion replacement, the patient should be given the benefit of the doubt and should be treated with intravenous hydrocortisone.

Summary

The fundamentals of adrenocortical function are discussed.

The modifying role of anesthesia is presented.

The behavior of patients with iatrogenic adrenal insufficiency undergoing relatively minor surgical interventions with resulting acute adrenal insufficiency due to lack of maintenance of adrenocortical therapy is described.

The beneficial effects of corticosteroid therapy in patients with known adrenocortical insufficiency undergoing major surgical procedures are also described.

Adrenocortical exhaustion due to sevère surgical trauma is still questionable but, in case of doubt, the intravenous administration of hydrocortisone is recommended.

References

1. Fraser, C. G., F. S. Preuss & W. D. Bigford. 1952. Adrenal atrophy and irreversible shock associated with cortisone therapy. J. Am. Med. Assoc. **149:** 1542.
2. Lundy, J. S. 1953. Cortisone problems involving anesthesia. Anesthesiology. **14:** 376.
3. Salassa, R. M., W. A. Bennett, F. R. Keating, Jr. & R. G. Sprague. 1953. Postoperative adrenal insufficiency—occurrence in patients treated with cortisone. J. Am. Med. Assoc. **152:** 1509.
4. Lewis, L., R. F. Robinson, J. Yee, L. A. Hacker & G. Eisen. 1953. Fatal adrenal cortical insufficiency precipitated by surgery during prolonged continuous cortisone therapy. Ann. Internal Med. **39:** 116.
5. Selye, H. 1951. The general adaptation syndrome and the diseases of adaptation. Am. J. Med. **10:** 549.
6. Sayers, G. 1950. The adrenal cortex and homeostasis. Physiol. Revs. **30:** 241.
7. DeGroot, J. & G. W. Harris. 1950. Hypothalamic control of anterior pituitary gland and blood lymphocytes. J. Physiol. **111:** 335.
8. Harris, G. W. 1951. Neural control of pituitary gland. Brit. Med. J. **2:** 627.
9. Schwartz, E. 1956. Uses of hormones in the treatment of allergic diseases. N. Y. State J. Med. **56:** 570.
10. Howard, J. M., R. E. Peterson, J. M. Olney, J. P. Frawley & S. Guerra. 1955. Adrenal function in the combat casualty. Arch. Surg. **71:** 47.

11. Nicholas, J. A., P. D. Wilson & C. J. Umberger. 1955. A comparison of urinary neutral 17-ketosteroid excretion with other fractions in operations upon the bones and joints. Surg. Gynecol. Obstet. **100:** 387.
12. Moore, F. D. 1955. Studies in surgical endocrinology. Ann. Surg. **141:** 145.
13. Sandberg, A. A., K. Eik-Nes, L. T. Samuels & F. H. Tyler. 1954. The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man. J. Clin. Invest. **33:** 1509.
14. Klein, R., C. Papadatos, J. Fortunato & C. Byers. 1955. Acid-hydrolyzable corticoids of serum. J. Clin. Endocrinol. and Metabolism. **15:** 215.
15. Elman, R., T. E. Weichselbaum, J. C. Moncrief & H. W. Margraf. 1955. Adrenal cortical steroids following elective operations; quantitative studies in the peripheral plasma of 17-hydroxy and 17-desoxycorticosteroids. Arch. Surg. **71:** 697.
16. Laidlaw, J. C., W. J. Reddy, D. Jenkins, N. A. Haydar, A. E. Renold & G. W. Thorn. 1955. Advances in the diagnosis of altered states of adrenocortical function. New Engl. J. Med. **253:** 747.
17. Thorn, G. W., P. H. Forsham, F. T. Prunty & A. G. Hills. 1948. A test for adrenal cortical insufficiency. The response to pituitary adrenocorticotropic hormone. J. Am. Med. Assoc. **137:** 1005.
18. Perlmutter, M. 1956. Rapid test for adrenocortical insufficiency. J. Am. Med. Assoc. **160:** 117.
19. Siker, E. S., E. Lipschitz & R. Klein. 1955. The effect of preanesthetic medications on the blood level of 17-hydroxycorticosteroids. Ann. Surg. **143:** 88.
20. Traina, V., C. L. Burstein, B. J. Ciliberti & E. A. Rovenstine. 1953. Pituitary-adrenal response to surgical trauma and anesthesia. I. The eosinopenic response. Anesthesiology. **14:** 449.
21. Tyler, F. H., C. D. Schmidt, K. Eik-Nes, H. Brown & L. T. Samuels. 1954. The role of the liver and the adrenal in producing elevated plasma 17-hydroxycorticosteroid levels in surgery. J. Clin. Invest. **33:** 1517.
22. Steenburg, R. W. & W. F. Ganong. 1955. Observations on the influence of extra-adrenal factors on circulating 17-hydroxycorticoids in the surgically stressed, adrenalectomized animal. Surgery. **38:** 92.
23. Papper, E. M. 1955. Renal function during general anesthesia. Bull. N. Y. Acad. Med. **31:** 446.
24. Papper, E. M. 1953. Renal function during general anesthesia and operation. J. Am. Med. Assoc. **152:** 1686.
25. Habif, D. V., E. M. Papper, H. F. Fitzpatrick, P. Lowrance, C. McC. Smythe & S. E. Bradley. 1951. Renal and hepatic blood flow, glomerular filtration rate and urinary output of electrolytes during cyclopropane, ether, and thiopental anesthesia. Surgery. **30:** 241.
26. Briggs, F. N & P. L. Munson. 1955. Studies on the mechanism of stimulation of ACTH secretion with the aid of morphine as a blocking agent. Endocrinology. **57:** 205.
27. Porter, R. W. 1953. Hypothalamic involvement in pituitary-adrenocortical response to stress stimuli. Am. J. Physiol. **172:** 515.
28. Hetzel, B. S., W. W. Schottstaedt, W. J. Grace & H. G. Wolff. 1955. Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man. J. Clin. Endocrinol. Metabolism. **15:** 1057.
29. Nicholas, J. A., C. L. Burstein, C. J. Umberger & P. D. Wilson. 1955. Management of adrenocortical insufficiency during surgery. Arch. Surg. **71:** 737.
30. Hayes, M. A. 1954. Shock and the adrenocortex. Surgery. **35:** 174.
31. Rukes, J. M., R. H. Orr, P. H. Forsham & M. Galante. 1955. The use of intravenous hydrocortisone in major surgery. Ann. N. Y. Acad, Sci. **61**(2): 448.
32. Howland, W. S., O. Schweizer, C. P. Boyan & A. C. Dotto. 1956. Treatment of adrenal cortical insufficiency during surgical procedures. J. Am. Med. Assoc. **160:** 1271.

HYPOTENSION AND THE AUTONOMIC NERVOUS SYSTEM*

By D. M. Aviado, Jr.

Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Among the many hazards that threaten a patient under general anesthesia, one that has aroused considerable interest is the potential development of systemic arterial hypotension. When hypotension is detected, the anesthesiologist is confronted with problems relating to its causation and therapy. In the course of arriving at some decision, he encounters various interrelationships between the hemodynamic factors for hypotension and the autonomic nervous system; these interrelationships are discussed in this paper. Other aspects of hypotension (the causes and treatment of which are not related to the autonomic nervous system) have been recently reviewed by Raab[1] and Judson.[2]

The Role of the Autonomic Nervous System in the Causation of Hypotension

In hemodynamic terms low arterial blood pressure is the outcome of a reduction in cardiac output and/or a reduction in total vascular resistance. The autonomic nervous system causes hypotension by two primary mechanisms: (1) cardiac slowing (as a result of increased vagal tone), which primarily reduces cardiac output; and (2) peripheral vasodilatation (as a result of decreased sympathetic tone), which directly reduces vascular resistance and indirectly reduces cardiac output by diminution of venous return (FIGURE 1). These dual effects of peripheral vasodilatation should not be interpreted to mean that hypotension cannot occur by vasodilatation alone without an accompanying reduction in cardiac output. There are powerful baroreceptor reflexes (discussed later in this paper) that can stimulate the heart when venous return is reduced; as a consequence, cardiac output during peripheral vasodilatation is usually unchanged or is even increased.

The ultimate causes for the hemodynamic changes during the hypotension of anesthesia can be understood only after a thorough examination of the different procedures related to the administration of the anesthetic and to the surgical operation for the individual patient. General anesthetics have direct actions on the autonomic nervous system, such as stimulation of the vagal medullary center by cyclopropane, depression of the vasoconstrictor medullary center by chloroform and ether, and blockade of autonomic ganglia by ether.[3, 4] However, such actions cannot be the sole cause of hypotension because the general anesthetics are known to depress directly the contractility of heart muscle.[5–7]

* Experiments reported in this paper were supported by a grant from the Office of the Surgeon General, Department of the Army, Washington, D. C., under Contract No. DA-49-007-MD-200.

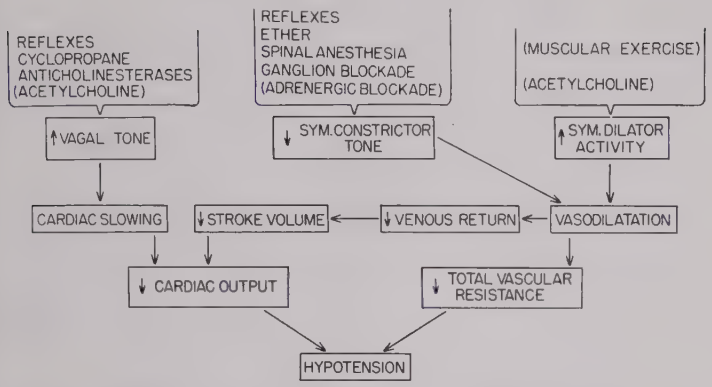

FIGURE 1. Role of the autonomic nervous system in the causation of systemic arterial hypotension. Other factors (such as bleeding, pre-existing disease, and anoxia) not primarily involving the autonomic nervous system have been omitted.

Other drugs, such as anticholinesterases, spinal anesthetics, and ganglion-blocking agents, exert important actions limited to the autonomic nervous system. Although they do not depress directly the myocardium and vascular smooth muscle, their effects extend to other organs innervated by the sympathetic and parasympathetic nervous system (eye, salivary gland, bronchi, intestine, bladder, and other organs). Surgical manipulations of various visceral organs are known to cause reflex cardiac slowing and vasodilatation. The cardiovascular reflexes will be reviewed in the next two sections in terms of the reflexes that cause hypotension and those that compensate for the hypotension initiated by any cause.

The Role of Cardiovascular Reflexes in the Causation of Hypotension

In a recent review,[8] the known reflexes are classified according to their pattern of stimulation or inhibition of the medullary centers controlling heart rate, vasomotor tone, and respiration. Four types are identified as follows: perfect or imperfect inhibition, and pure or impure stimulation (FIGURE 2).

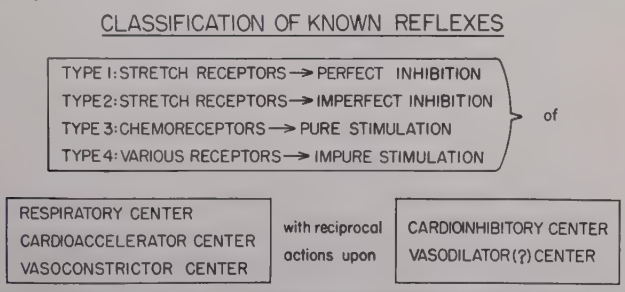

FIGURE 2. Patterns of response elicited by activation of known reflexes. The specific reflexes belonging to each type are tabulated in a recent review article.[8]

The actions of the various reflexes in terms of the cardiovascular system consist of one or two of the following responses: bradycardia, tachycardia, vasoconstriction, and vasodilatation. From the examples of reflexes initiating each of the various responses (FIGURE 3) it is apparent that, although the chemoreceptors are limited only to the carotid and aortic bodies, the baroreceptors (stretch receptors sensitive to changes in blood pressure) are scattered all over the cardiovascular system.

There are several review articles covering the participation of reflexes in anesthesia.[9, 12] The following procedures have been reported to cause cardiac slowing or arrhythmias accompanied by hypotension: inhalation of ether;[13] intubation or mechanical irritation of trachea and bronchi;[14-16] irritation of the pleura;[17] traction upon the pulmonary hilus;[18, 19] irritation of the pericardium;[20, 21] resection of the esophagus;[22] scraping and spreading of the ribs;[22] and traction of abdominal and pelvic visceral organs.[23-25] In all of the above situations, the nature of the procedure warrants the conclusion that the responses are reflex in nature. However, there are two uncertainties. First, aside from the cardiac slowing, is there additional vasodilatation contributing to the observed hypotension? Second, what is the normal function of the receptors activated by the mechanical manipulation, or which known receptors (FIGURE 3) are responsible for the response? Answers to these questions are not yet available from clinical studies.

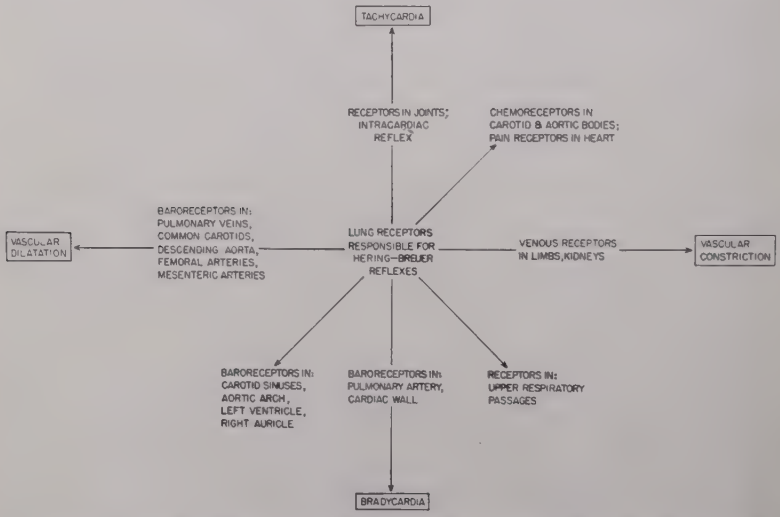

FIGURE 3. Known receptors grouped according to their effects on heart rate and vasomotor tone. The 4 groups of receptors on the vertical and horizontal arrows influence either heart rate or vasomotor tone. The 3 other groups on the diagonal arrows influence both functions. Note that there is no example of a reflex that causes combined tachycardia and vasodilatation. The central group represents receptors that primarily affect respiration and have insignificant circulatory action.

Additional measurements of blood flow and of vascular resistance during the various procedures will aid in answering the first question. As to identification of the specific receptors, appropriate denervation and oscillographic recordings of nerve potentials are practicable only in animals. Until pertinent information becomes available, the best explanation for the reflex hypotension seen clinically is as follows: the known receptors (baroreceptors and pain receptors in the heart, in the pulmonary vessels, and in the aorta and its branches) are accidentally stimulated by mechanical manipulation of the various organs. Such an explanation is, of course, limited by the possibility that there may be receptors (not necessarily baroreceptors) yet undiscovered that may explain the reflex hypotension.

Baroreceptor Reflexes That Compensate for Hypotension of Acute Blood Loss

Although numerous humoral and nervous factors regulating circulation are known to compensate for hemorrhage, the relative roles of the individual factors are not known.[26–28] The experiments reported here are attempts to investigate the relative importance of the various baroreceptor reflexes in the immediate adjustment to hemorrhage.*

Methods. Dogs under morphine and chloralose anesthesia were bled from the femoral artery in amounts expressed in percentage of total blood volume (initially measured by the Evans Blue dilution technique).[29] This blood was heparinized for subsequent return into the femoral vein. The following measurements were continuously recorded on a kymograph and on an inkwriting oscillograph for at least 10 minutes before and after each bleeding: (1) aortic blood pressure, by means of a Lilly capacitance manometer;[30] (2) vena cava pressure, via a catheter with a capillary saline manometer; (3) electrocardiogram; (4) rate and depth of respiration, by an automatic tidal volume recorder;[31] and (5) cardiac output, by the Fick principle, based on oxygen consumption and oxygen contents of pulmonary and femoral arterial blood samples. It was possible to perform 3 or more bleedings of varying amounts on each of 29 dogs, before and after one or more of the following procedures: adrenalectomy; denervation of carotid receptors (cutting the nerve of Hering); denervation of aortic receptors (cutting the aortic depressor nerve by the method of Kock);[32] denervation of cardiopulmonary baroreceptors (by vagotomy); pithing of the spinal cord; and intravenous injection of atropine sulfate, 0.2 mg./kg.

Immediate effects of bleeding. A typical picture of the effects of loss of about 8 per cent of the total blood volume is represented in FIGURE 4. The maximum fall in aortic and venous pressures, as well as the reduction in cardiac output, can be regarded as the direct consequences of a reduction in blood volume. The accompanying changes (respiratory stimulation, increased total peripheral vascular resistance, tachycardia, and recovery of aortic blood pressure) are compensatory in nature. The average cardio-

* Experiments were performed with G. W. Peskin, R. O. Bell, Jr., and G. L. Turnbull.

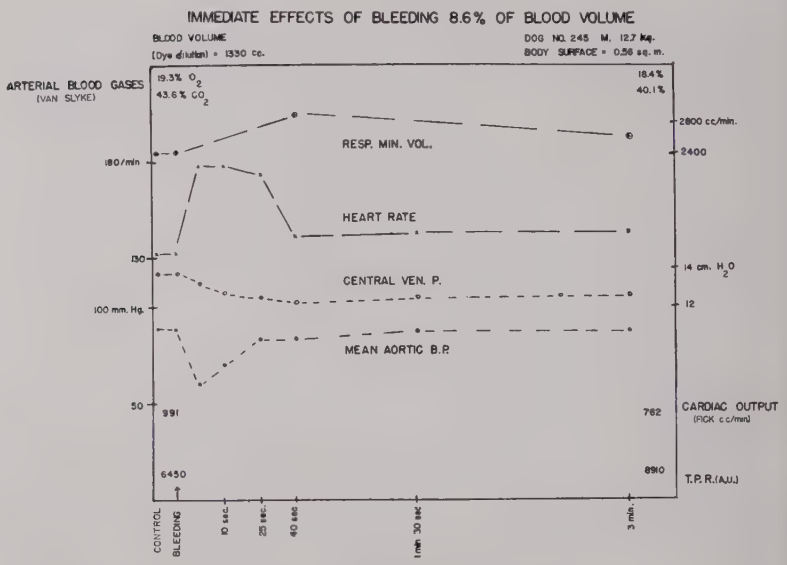

FIGURE 4. Typical response to bleeding.

vascular changes following 33 bleedings in 11 dogs are summarized in FIGURE 5.

It is conspicuous that the recovery of aortic blood pressure was almost always complete when blood losses amounted to 5 to 10 per cent of initial blood volume. Losses greater than 20 per cent were followed by spontaneous recovery to within 15 per cent of control aortic blood pressure. The severity of the tachycardia was proportional to the degree of hemorrhage.

Mechanisms for tachycardia. It is generally known that the fall in aortic blood pressure causes reflex tachycardia by inactivation of the baroreceptors in the carotid sinuses and in the aortic arch. For two reasons this is not the complete explanation for the tachycardia of hemorrhage: (1) the period of tachycardia response outlasted the duration of aortic hypotension following a bleeding (FIGURE 4); and (2) in 8 dogs in which the carotid sinus and aortic nerves were cut, the tachycardia response could still be induced by bleeding (FIGURE 6). The only method found to eliminate the tachycardia response completely was to denervate, by cervical vagotomy, not only the carotid and aortic baroreceptors, but also similar receptors in the heart and pulmonary vessels. The cutting of motor cardiac fibers could not fully explain the effects of vagotomy because atropinization did not prevent the tachycardia. Thus it was evident that the immediate tachycardia following hemorrhage was a reflex response activated by the fall in blood pressure in the carotid sinuses, in the aortic arch, in the heart, and in the pulmonary vessels.

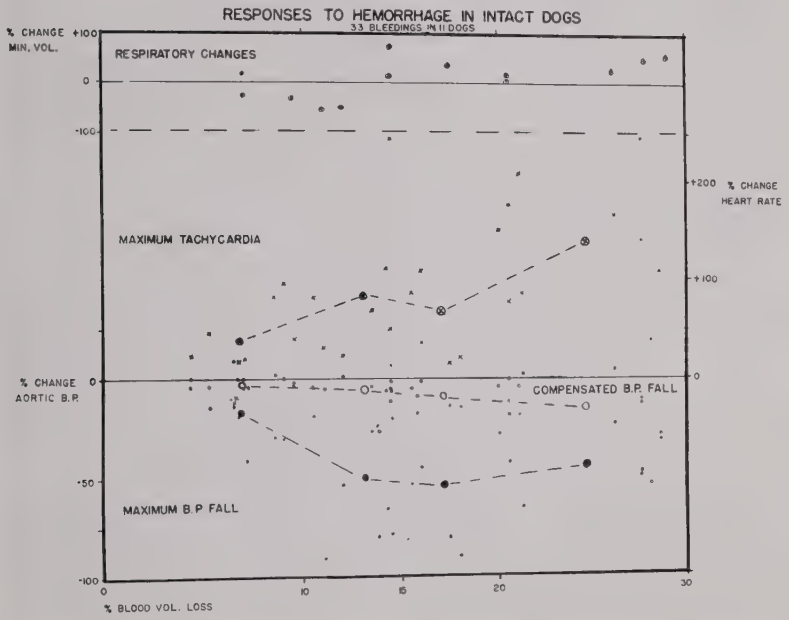

FIGURE 5. Effects of amount of blood loss (percentage of initial blood volume on abscissa) on percentage change of respiratory minute volume, percentage change of heart rate, maximum percentage fall in aortic pressure (solid circles) and percentage fall within 2 minutes after bleeding (compensated fall). Connected points refer to average measurements of four groups: bleeding up to 10 per cent; 10 to 15 per cent; 15 to 20 per cent; and greater than 20 per cent.

Mechanisms for recovery of aortic blood pressure. Combined denervation of the carotid, aortic, pulmonary, and cardiac receptors resulted in an incomplete recovery of aortic blood pressure following hemorrhage (FIGURE 7). This recovery could not have been entirely dependent upon the occurrence of tachycardia because atropinization significantly reduced the tachycardia response, although the recovery of blood pressure was complete. The major cause for the recovery in blood pressure was arterial vasoconstriction, the presence of which was demonstrable by leg perfusion experiments. The slight recovery in pressure after complete denervation of the baroreceptors can be attributed to humoral factors[33] and to local vascular adjustments.[34, 35]

Summary. Baroreceptor reflexes arising from the carotid sinuses, the aortic arch, the heart, and the lungs are responsible for the tachycardia and vasoconstriction following bleeding of anesthetized dogs. These reflexes allow the immediate recovery of the hypotension initiated by a primary reduction in circulatory blood volume.

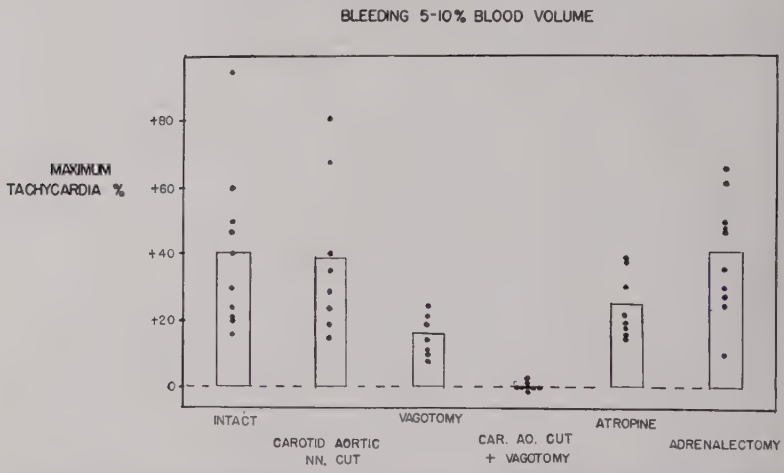

FIGURE 6. Maximum percentage of tachycardia following bleeding of 10 intact dogs, 8 after carotid-aortic denervation, 7 after vagotomy, 8 after combined vagotomy and carotid-aortic denervation, 8 after atropine sulfate, and 10 after adrenalectomy. The top of each block represents the average response of the represented measurements for the group.

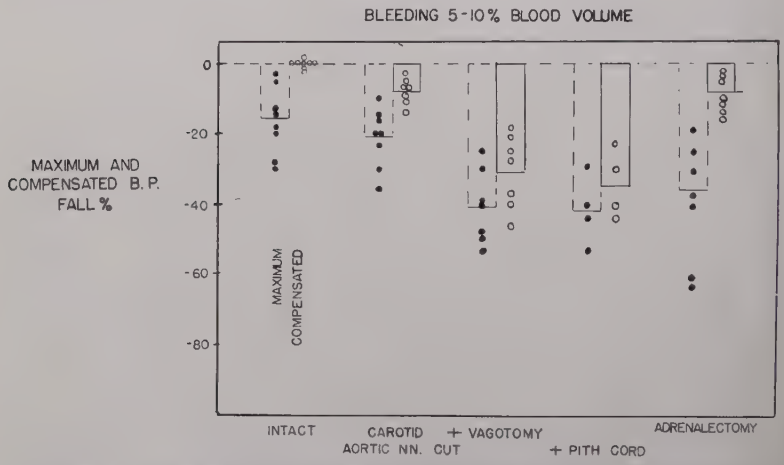

FIGURE 7. Maximum and compensated percentage fall in aortic blood pressure of the same groups of dogs represented in FIGURE 6. An additional group of 4 dogs with spinal cords pithed is included.

Management of Hypotension

The complications resulting from hypotension can generally be explained by a reduction in blood flow to various organs (FIGURE 8). The dependence of blood flow on aortic pressure is, of course, modified by local changes in vascular resistance that vary, depending on the exact cause of hypotension. The organs that are known to possess powerful sympathetic vasoconstrictor innervation (the kidney, the splanchnic area, and the limbs) are threatened by additional reflex vasoconstriction. The brain possesses local compensatory mechanisms that prevent the flow from becoming proportionally decreased because of local vasodilatation when aortic pressure is decreased.[36] The heart possesses a similar adjustment: a reduction in coronary blood flow due to hypotension will induce myocardial anoxia, a condition that will bring about a compensatory increase in coronary blood flow.[37] If this adjustment is insufficient to correct myocardial anoxia, then there is a reduction in cardiac output that further exaggerates the fall in blood pressure. Myocardial anoxia in turn increases the susceptibility of the heart to cardiac arrest and to fibrillation, particularly in the presence of reflexes that initiate cardiac arrhythmias.[38, 39]

The correction of the hypotension is desirable in order to avoid the complications mentioned above. The role of the baroreceptor reflexes in

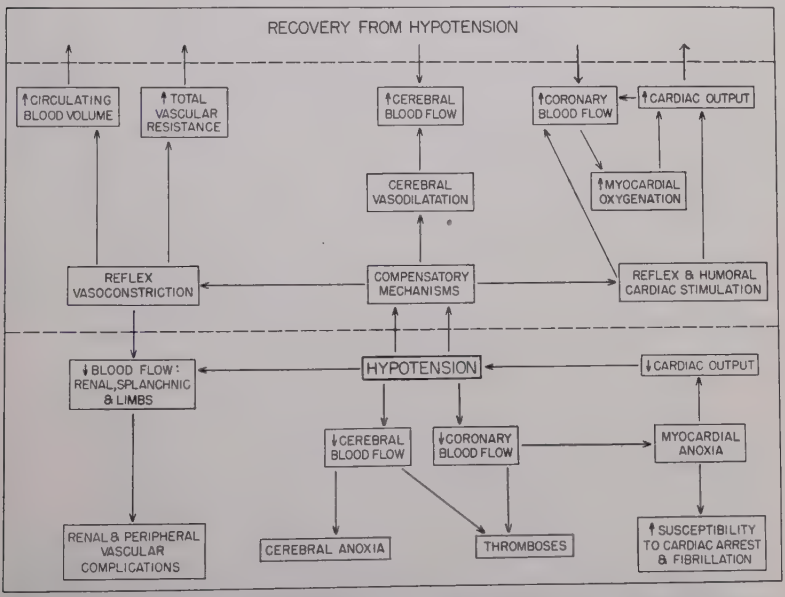

FIGURE 8. Potential hazards following arterial hypotension (lower half); compensatory mechanisms responsible for spontaneous recovery from hypotension (upper half).

bringing about the recovery of the aortic blood pressure has been discussed earlier in this paper and is summarized in FIGURE 8. The rise of blood pressure is the immediate outcome of reflex vasoconstriction and of reflex and humoral (epinephrine-stimulated) cardiac stimulation. There is general improvement of cerebral and coronary blood flow as a result of the rise in pressure. With regard to coronary circulation, an additional factor is the cardiac stimulation, which is always accompanied by improvement in coronary circulation.

In all instances of hypotension, the primary concern is the recognition and correction of the initiating cause. In some instances correction is simple and practicable, involving such measures as: blood transfusion for hemorrhage; reducing the amount of inhalation anesthetic if the patient is in deep narcosis; improving oxygenation by intubation and assisted respiration if the airway is obstructed; and administering sufficient atropine if intense cardiac slowing is initiated by surgical manipulation. Some situations do not allow immediate removal of the cause, for example, severe hypotension following such procedures as: high spinal anesthesia, massive doses of ganglion-blocking agents, intravenous procaine, or prolonged thoracic surgical operations. In these instances, sympathomimetic amines are ideal for bringing about a rise in aortic blood pressure.

Comparative Hemodynamic Effects of Sympathomimetic Amines

All sympathomimetic amines, with the exception of isoproterenol and methoxyphenamine, are powerful systemic vasoconstrictors. In sufficient doses, they cause systemic arterial hypertension with reflex bradycardia and vasodilatation (via carotid-aortic baroreceptors). This is the only action common to all pressor amines; the other hemodynamic effects vary depending on the individual amine.

The major differences schematized in FIGURE 9 can be illustrated by con-

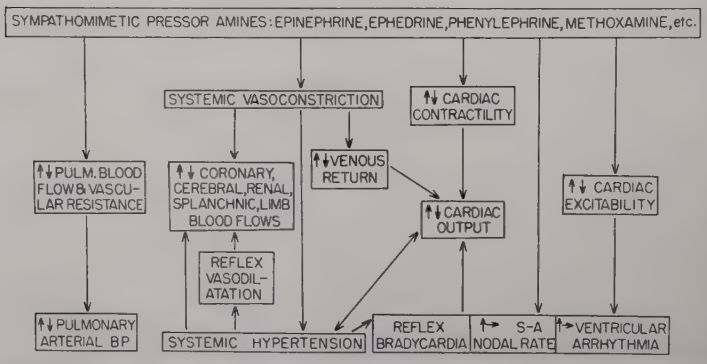

FIGURE 9. Hemodynamic effects of sympathomimetic pressor amines. Similar and dissimilar effects are emphasized.

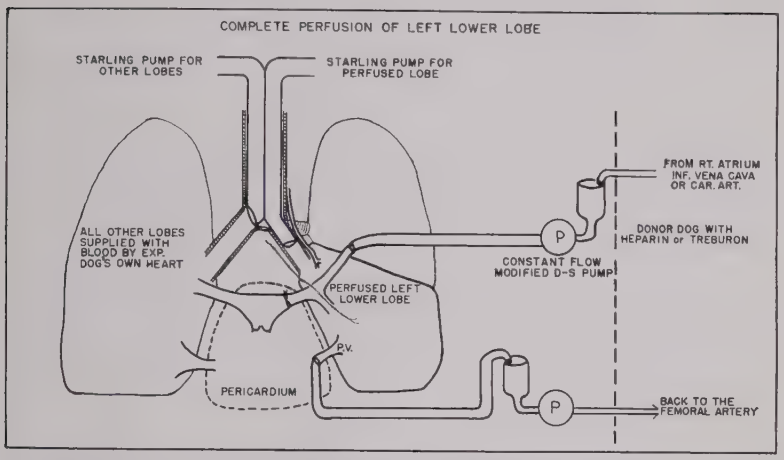

FIGURE 10. Method for demonstrating the local effects of drugs on the perfused lung vessels of the anesthetized dog. The left lower lobe is supplied by a Dale-Schuster pump with blood from a donor dog. Vasoconstriction is manifested by a rise in perfusion pressure, since blood flow is kept constant. The changes in arterial pressure of the other lobes supplied by the animal's own heart reflect changes in cardiac output, as well as changes in vascular resistance.

trasting the effects of epinephrine and of methoxamine. Epinephrine increases sino-auricular rate, cardiac force of contraction, ventricular excitability, and cardiac output, whereas methoxamine does not increase them.[40–43] Comparative effects of the pressor amines upon the various vascular beds are not yet completely known. For the pulmonary circulation, the information has been derived from anesthetized dogs in which pulmonary arterial blood pressure and lung perfusion pressure were measured following various sympathomimetic amines (the method is illustrated in FIGURE 10). The results so far indicate that the sympathomimetic amines most frequently used by anesthesiologists are pulmonary vasoconstrictor agents, with the exception of methoxamine, which is a pulmonary hypotensive drug (TABLE 1). This particular difference is worth remembering when

TABLE 1

COMPARATIVE EFFECTS OF VARIOUS SYMPATHOMIMETIC AMINES ON THE PULMONARY CIRCULATION

Pressor amines I.V. in systemic equipressor doses (anesthetized dogs)	Pulmonary arterial blood pressure (supplied by cardiac action)	Local action on lobe (perfused by D-S pump)	Probable role of increased pulmonary blood flow*
Epinephrine (Suprarenin)	↑ ↑	constrict	+
Norepinephrine (Levophed)	↑ ↑	constrict	+ or 0
Ephedrine	↑ ↑	constrict	+
Metaraminol (Aramine)	↑ ↑	constrict	0
Phenylephrine (Neosynephrine)	↑ ↑	constrict	0
Methoxamine (Vasoxyl)	↓	not constrict	0

* From experiments of other investigators involving measurements of cardiac output.

there is some suspicion that pulmonary edema may develop in connection with the use of sympathomimetic amines.

Summary

The role of circulatory reflexes in the causation of hypotension is reviewed. The baroreceptors in the carotid sinuses, aortic arch, heart, and lungs can compensate for aortic hypotension of hemorrhage by inducing vasoconstriction and tachycardia. Activation of other receptors can actually bring about bradycardia and vasodilatation.

The hemodynamic effects of sympathomimetic amines are reviewed. Their primary effects on the heart and special vascular beds, as well as their secondary reflex effects, are compared. Although the systemic vasoconstrictor actions of all these amines are alike, their effects on the heart and pulmonary circulation are different.

References

1. Raab, W. 1955. Neurogenic and hormonal hypotension. Anesthesiology. **16:** 781–794.
2. Judson, W. E. 1953. Hypotension: Physiologic mechanisms and treatment. Med. Clin. N. Amer. **37:** 1313–1339.
3. Larrabee, M. G. & J. M. Posternak. 1952. Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. J. Neurophysiol. **15:** 91–114.
4. Norman, N. & B. Lofstrom. 1955. Interaction of *d*-tubocurarine, ether, cyclopropane and thiopental on ganglionic transmission. J. Pharmacol. Exptl. Therap. **114:** 231–239.
5. Brewster, W. R., Jr., J. J. P. Isaacs & T. Wainø-Andersen. 1953. Depressant effect of ether on myocardium of the dog and its modification by reflex release of epinephrine and nor-epinephrine. Am. J. Physiol. **175:** 399–414.
6. Woods, E. F. & J. A. Richardson. 1955. A survey of agents producing cardiovascular manifestations of epinephrine discharge. J. Pharmacol. Exptl. Therap. **114:** 445–452.
7. Price, H. L. & M. Helrich. 1955. The effect of cyclopropane, diethyl ether, nitrous oxide, thiopental, and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation. J. Pharmacol. Exptl. Therap. **115:** 206–216.
8. Aviado, D. M., Jr., & C. F. Schmidt. 1955. Reflexes from stretch receptors in blood vessels, heart and lung. Physiol. Revs. **35:** 247–300.
9. Scurr, C. F. 1950. Reflex circulatory disturbances during anaesthesia. Anaesthesia. **5:** 67–79.
10. Harken, D. E. & L. R. Norman. 1950. The control of cardiac arrhythmia during surgery. Anesthesiology. **11:** 321–327.
11. Reid, C. L., H. E. Stephenson, Jr. & J. W. Hinton. 1952. Cardiac arrest. Arch. Surg. **64:** 409–420.
12. Bergner, R. P. 1955. Cardiac arrest: some etiological considerations, with reports of seventeen cases. Anesthesiology. **16:** 177–189.
13. Johnstone, M. 1951. General anaesthesia and cardiac inhibition. Brit. Heart J. **13:** 47–55.
14. Reid, J. C. & D. E. Brace. 1940. Irritation of the respiratory tract and its reflex effect upon the heart. Surg. Gynecol. Obstet. **70:** 157–162.
15. Adams, H. D. & L. V. Hand. 1942. Twenty minute cardiac arrest with complete recovery. J. Am. Med. Assoc. **118:** 133–135.
16. Clowes, G. H. A., A. L. Hopkins & F. A. Simeone. 1955. A comparison of the physiological effects of hypercapnia and hypoxia in the production of cardiac arrest. Ann. Surg. **142:** 446–460.
17. Capps, J. A. & D. D. Lewis. 1907. Observations upon certain blood-pressure

lowering reflexes that arise from irritation of inflamed pleura. Trans. Am. Assoc. Physicians. **22:** 635–666.
18. Soave, F. 1950. The anesthetic blocking of the vagus, the sympathetic and the phrenic at the neck in thoracic surgery—its protective action on blood pressure. J. Thoracic Surg. **19:** 157–166.
19. Dodrill, F. D., E. Hill & R. Gerisch. 1952. Some physiologic aspects of the artificial heart problem. J. Thoracic Surg. **24:** 134–150.
20. Leriche, R., R. Fontaine & J. Kunlin. 1932. Étude expérimentale de la (sensibilité du péricarde, de l'épicarde et d'endocarde. Compt. rend. soc. biol.) **110:** 297–298.
21. Chernikovskii, V. N. 1943. Refleks interotsentorov perikarda. II. Bull. biol. méd. exptl. U. S. S. R. **15:** 31–35.
22. Crandell, D. L. & J. F. Artusio, Jr. 1953. Cardiovascular reflexes during intrathoracic surgery. Current Researches Anesthesia & Analgesia. **32:** 227–241.
23. Owen, S. E. 1932. A study of viscerocardiac reflexes. I. The experimental production of cardiac irregularities by visceral stimulation. Am. Heart J. **8:** 496–506.
24. Burstein, C. L., A. Jackson, H. F. Bishop & E. A. Rovenstine. 1950. Curare in the management of autonomic reflexes. Anesthesiology. **11:** 409–421.
25. Stephen, C. R., W. K. Nowill & R. Martin. 1953. Diagnosis and treatment of hypotension during anesthesia. Anesthesiology. **14:** 180–194.
26. McDowall, R. J. S. 1938. The Control of the Circulation of the Blood. Longmans, Green. London, England.
27. Bazett, H. C. 1941. Blood Volume in Relation to the Circulation. MacLeod's Physiology in Modern Medicine. Mosby. St. Louis, Mo.
28. Wiggers, C. J. 1942. The present status of the shock problem. Physiol. Revs. **22:** 74–123.
29. Gibson, J. G., Jr. & W. A. Evans, Jr. 1937. Clinical studies of blood volume: clinical application of method employing azo dye "Evans blue" and spectrophotometer. J. Clin. Invest. **16:** 301–316.
30. Peterson, L. H., R. D. Dripps & G. C. Risman. 1949. A method for recording arterial pressure pulse and blood pressure in man. Am. Heart J. **37:** 771–782.
31. Peck, H. M. & W. S. Waller. 1948. A tidal volume recorder for anesthetized dogs. J. Lab. Clin. Med. **33:** 784–788.
32. Koch, E. 1931. Die Reflektorische Selbststeuerung des Kreislaufs. T. Steinkopff. Dresden, Germany.
33. Zweifach, B. W. & F. Shorr. 1948. Factors regulating blood pressure. Josiah Macy, Jr. Foundation. New York, N. Y.
34. Bayliss, W. M. 1923. The Vaso-Motor System. Longmans, Green. London, England.
35. Folkow, B. 1949. Intravascular pressure as a factor regulating the tone of the small vessels. Acta Physiol. Scand. **17:** 289–310.
36. Dewar, H. A., S. G. Owen & A. R. Jenkins. 1953. Influence of tolazoline hydrochloride (Priscol) on cerebral blood flow in patients with mitral stenosis. Lancet. **1:** 867–870.
37. Schmidt, C. F. 1951. The pharmacological basis of the therapy of coronary disease. Trans. Am. Coll. Cardiol. **1:** 89–98.
38. Stephenson, H. E., Jr., C. Reid & J. W. Hinton. 1953. Some common denominators in 1200 cases of cardiac arrest. Ann. Surg. **137:** 731–744.
39. Sloan, H. E. 1950. The vagus nerve in cardiac arrest. Surg. Gynecol. Obstet. **91:** 257–264.
40. Hjort, A. M., L. O. Randall & E. J. de Beer. 1948. The pharmacology of compounds related to 2,5-dimethoxy phenethyl amine. I. The ethyl, isopropyl and propyl derivatives. J. Pharmacol. Exptl. Therap. **92:** 283–290.
41. Goldberg, L. I., M. de V. Cotten, T. D. Darby & E. V. Howell. 1953. Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines. J. Pharmacol. Exptl. Therap. **108:** 177–185.
42. Lahti, R. E., I. C. Brill & E. L. McCawley. 1955. The effect of methoxamine hydrochloride on cardiac rhythm. J. Pharmacol. Exptl. Therap. **115:** 268–274.
43. Wnuck, L. A., C. H. Ellis, S. V. Guzman, S. Bellet, J. W. West & D. M. Aviado, Jr. 1955. Unpublished observations.

PROTECTIVE MECHANISMS IN SHOCK*

By B. W. Zweifach and S. G. Hershey

Departments of Pathology and Anesthesiology, New York University, Bellevue Medical Center, New York, N. Y.

An important unresolved problem in the operative management of surgical patients is that posed by the seemingly inevitable progression of severe, protracted hypotension to a "point of no return," despite blood replacement and drug therapy. During the early phases of the hypotensive reaction to hemorrhage, compensatory readjustments prevail and the condition can readily be alleviated by blood replacement. With time, however, there develops a set of decompensatory reactions that progressively undermine the precarious homeostatic balance and make the individual less responsive to blood replacement measures. In experimental shock it is possible, with graded hemorrhage, to achieve a "state of irreversibility" that resembles the condition encountered following various traumatic injuries. More recently, it has been found possible to combat successfully the lethal tendency even in this form of severe shock.[1-3] This report is concerned with experimental findings in this area.

An effective approach to the problem has been to use the behavior of the terminal vascular bed as an index of the general trend of circulatory readjustment measures.[4] The pattern of vascular behavior has indicated the existence of two discrete phases in response to both hemorrhage and trauma. Initially, there appears a series of compensatory adjustments characterized by increased vasomotor activity, heightened sensitivity, and selective restriction of blood flow to the most central and direct channels. The attendant vasoconstriction is not uniform, either in degree or extent; it appears earliest in the skin, skeletal musculature, and the kidneys, and it is sustained by stimuli from central chemoreceptors and baroreceptors without direct reference to the status of the circulation through the tissue proper. In instances where these readjustments are sufficient to sustain peripheral blood flow at near normal levels, the metabolic effects associated with more profound shock are circumvented. Recovery, either spontaneous or following transfusion, is invariable. However, when the blood pressure drops to extremely low levels despite maximal compensatory activities, widely different cellular disturbances occur and ultimately result in serious derangement of the circulation. With protracted hypotension, the compensatory behavior is progressively replaced in the vascular bed by a decompensatory tendency, manifested by a failure to sustain the ischemic restricted pattern of blood flow, by a hyporeactivity of the muscular elements, and by a venous stagnation to the point of almost complete stasis. The longer the decompensatory tendency is permitted to develop, the less favorable is the prognosis for recovery as a result of blood replacement

* The work described in this paper was supported in part by a grant from the Life Insurance Medical Research Fund, New York, N. Y., and by a grant from the Joseph and Helen Yeamans Levy Foundation, Beth Israel Hospital, New York, N. Y.

measures. Irreversibility is uniformly associated with a full quota of decompensatory activities.

During protracted shock the impairment of peripheral blood flow below levels compatible with aerobic metabolism leads uniformly to the development of characteristic pathological changes in particular sites. The severity and extent of the vascular and tissue damage can be shown to depend upon and to be influenced predictably by the experimental conditions employed. In many instances, these contributory or sustaining factors are directly responsible for setting into motion the vicious cycle culminating in circulatory collapse (TABLE 1). As we have become aware of the nature and sphere of action of such factors as anesthetic agents,[5] bacterial toxins,[6] tissue metabolites,[7] and the depletion of substances essential to cellular function,[8] specific measures have been designed to attenuate or to modify these circumstances and thereby to circumvent the lethal outcome of the syndrome. Each of these factors has been shown to contribute in different degree to the vascular collapse following stress and to affect different organs to a variable extent.

Regional differences in the extent and degree of vasoconstriction during stress are to be accounted for by differences in sympathetic innervation,[9] by the pattern of vascular distribution, by interanastomoses between arterial and venous vessels, and by peculiarities in the structural make-up of the capillary bed itself.[10] Two organs that are especially vulnerable to the curtailment of their blood supply are the liver and the small intestine. The liver, because its oxygen is supplied in large part by the portal vein, becomes hypoxic early in shock, following a marked drop in the oxygen tension of the portal vein blood and a reduction in the arterial blood supply by way of the hepatic artery.[11] The bowel, by virtue of the interanastomosing character of its peripheral blood channels, shows stagnation and stasis early in the hypotensive state, and it becomes in turn susceptible to the action of proteolytic enzymes and to bacterial products in the lumen of the intestine.[12]

TABLE 1

MECHANISMS RELATED TO IRREVERSIBILITY

(1) Impairment of peripheral circulation
  (a) Hyporeactivity
  (b) Depressed vasomotion
  (c) Increased capillary permeability
(2) Local "toxic" elements
  (a) Tissue metabolites
  (b) Diminished intrinsic tone of blood vessels
(3) Systemic "toxic" factors
  (a) Hepatic ferritin
  (b) Adenyl compounds
  (c) Bacterial products (endotoxins)
(4) Coronary insufficiency
(5) Damage to "reflex" receptors (chemoreceptors and baroreceptors)

Resistance to shock can be induced by pretreatment with autonomic blocking drugs, by the administration of certain antibiotics, and by increasing the tolerance of the host through a physiological adaptation to repeated exposure to sublethal trauma or bacterial endotoxins. Studies dealing with each of these separate aspects were carried out in both hemorrhagic and traumatic shock in the rat and in the dog.

It is interesting to note that, in each instance in which protection was afforded, the over-all improvement was characterized by the absence of vascular decompensation and pathology in the liver and bowel. This was especially true in relation to anesthetic agents and bacterial toxins.[13] More recent evidence has shown that fatal shock of an "irreversible" type following graded hemorrhage can be induced in the absence of significant bowel and liver pathology, a finding that would seem to indicate that the decisive factor or factors have not yet been identified.

Autonomic Blockade

Autonomic blockade, both surgical and chemical, has been found to influence favorably the course of the shock syndrome, presumably by blunting the intense peripheral vasoconstriction that develops. The clinical use of autonomic blocking drugs has been explored chiefly in relation to hypotensive anesthesia,[14] which has been claimed to be associated with a significant improvement during the postoperative course. The clinical trials differ from the experimental studies in animals in several respects. Drugs such as hexamethonium were used to bring the blood pressure to hypotensive levels prior to surgery. Blood was administered continuously to fill the dilated vascular bed and to maintain an adequate peripheral blood flow. The subsequent surgical trauma was therefore superimposed on a patient with a plethoric blood volume and a comparatively low blood pressure. The latter condition is also believed to lessen tissue bleeding during surgery. However, in addition to the mechanical effects of this regimen, there would appear to be an amelioration of the metabolic disturbances that usually accompany shock.

In laboratory animals, striking protection has been afforded by pretreatment with certain adrenergic and ganglionic blockers[15] that decrease the mortality following otherwise lethal shock situations. It was not possible to curtail the deleterious sequelae of the syndrome when these blocking drugs were administered either subsequent to the development of shock or together with blood transfusions. Examination of the several drugs that have been used successfully in protection experiments in animals reveals no common denominator to which their beneficial effects could be attributed. One of the earliest blocking agents shown to protect against both hemorrhagic and traumatic shock was the drug *N*-(2-chloroethyl)dibenzylamine hydrochloride (Dibenamine).[16] The principal pharmacological effect of this compound is that of adrenergic blockade.

It has been suggested that the beneficial action of blocking drugs resides

in their capacity to attenuate the vasoconstriction that develops during hypotension so as to permit more adequate perfusion of the tissues with blood despite the extremely low blood-pressure levels. This contention, however, is not in accord with the finding that pharmacological agents with an equivalent blocking action on vasomotor responses do not uniformly sustain the circulation during shock, despite a comparable diminution of arterial vasoconstriction. It can readily be appreciated that in drug-protected animals the deleterious effects of hypotension on the capillary circulation are not simply the consequences of a dissipation of the *vis a tergo* of the blood. In the pretreated individual, capillary blood flow is maintained efficiently despite reduction of the blood pressure to comparable levels. The essential feature of the protection would appear to be a diminution of the vasoconstriction mediated through neurogenic mechanisms, without interference with the intrinsic capacity of smooth muscle elements *per se* to readjust to changes in peripheral blood flow in the tissue proper. At least two factors have been identified in this regard: (1) the intrinsic tone of the smooth muscle elements, especially of the collecting venules, is not lost; (2) blood continues to be distributed through the proximal branches of the larger arterioles that re-enter the venous system without coursing through the extensive capillary network. This latter factor assists considerably in the maintenance of an unobstructed venous flow from the tissues.

The use of autonomic blocking drugs, particularly chlorpromazine, has brought to light a number of important features of the shock reaction. As previously indicated, the decompensatory reaction leading to irreversibility is usually associated with extensive congestion, stasis, and hemorrhage in the liver and in the small intestine. Both of these organs show a remarkable absence of pathological changes in animals pretreated with chlorpromazine. Surgical removal of the intestinal tract and of the liver almost completely circumvented the striking decompensation following hemorrhage, as evidenced by the absence of uptake of blood during protracted periods of drastic hypotension.[17] Nevertheless, irreversibility developed in these animals except when pretreatment with chlorpromazine was introduced.

In our initial experiments, a broad spectrum of autonomic blocking drugs was studied with respect to drum shock (TABLE 2). It can be seen that

TABLE 2

DRUGS INDUCING PROTECTION AGAINST DRUM SHOCK

Agent	Dose (mg./100 gm.)		Blocking action
Hexamethonium	1.0	I.V.	ganglionic
SC 2159 (Searle)	0.25	I.V.	ganglionic
Pendiomide dibromide	0.1	I.V.	ganglionic
Dibenzyline	0.02	S.C.	adrenergic
Lilly SY 14	0.2	I.P.	adrenergic
Chlorpromazine	1.25	I.M.	adrenergic C.N.S.
Sodium azide	0.04	S.C.	antihypertensive

particular members of each of the categories of pharmacological agents displayed protective potentialities. Despite the fact that agents having anticholinergic activity were uniformly without protective action, atropinized rats (2 mg./100 gm.) showed a more favorable response to trauma in that the survival rate was increased from 25 per cent to a level of 45 to 50 per cent. Other drugs in this category, including banthine and probanthine, actually intensified the shock response and decreased the amount of trauma that could be tolerated. Representative antihistaminic drugs were also studied since several investigators had shown that *N*-(2′-dimethylamino-2′-methyl) ethyl phenothiazine hydrochloride (Phenergan) had a beneficial influence on the survival following shock. It should be noted that many drugs with antihistamine activity likewise possess in varying degrees adrenergic and even cholinergic blocking properties. Thus Phenergan, in the dose employed, is an effective adrenergic blocking agent. When other drugs with more selective antihistaminic properties were employed (chlorprophenpyridamine maleate—Chlor-Trimeton), no protection was obtained.

A number of drugs with adrenergic blocking potentialities have been found to offer some degree of protection against drum trauma.[2, 15] Included in this group of agents are dibenzyline, 0153* and SY14*. Here again, other drugs with equivalent adrenergic blocking properties exerted no protective action. Ganglionic blocking drugs uniformly increased the percentage of survival following drum trauma. Hexamethonium was the least effective of the agents investigated. This may at first appear to be at variance with clinical findings where hexamethonium was the agent most frequently used in hypotensive anesthesia. However, the two situations are not comparable since, in surgical procedures, blood replacement is carried out continuously.

Several antihypertensive agents were examined. It was felt that drugs of this type, by weakening vasoconstrictor mechanisms, might circumvent the tissue changes leading to peripheral circulatory collapse. Sodium azide, in doses of 100 μg. just prior to drumming, was found to exert a moderate protective action; 53 per cent of the treated rats survived as compared with 35 per cent of the controls. Another antihypertensive agent, hydralazine hydrochloride (Apresoline), was given in doses of 1 to 2 mg./100 gm. body weight and was found to exert a deleterious, rather than a protective, action.

Among the centrally acting agents that have recently been found to influence the response to a wide variety of noxious stimuli, the chlorpromazine derivatives represent a new approach to the problem.[19] Chlorpromazine has been widely used as an adjunct to hypothermia, where its use was attended by a more favorable course following surgery and hemorrhage. The precise mechanism of its action in this regard is as yet unknown. When administered alone, chlorpromazine has a mild sedative action and has been found to potentiate the action of other anesthetic agents; this finding necessitated the use of smaller doses of pentobarbital in experiments

* Eli Lilly and Co., Indianapolis, Ind.

where anesthesia was required. It was necessary, therefore, to take this potentiation into consideration in evaluating the findings with chlorpromazine in hemorrhage. Since no anesthesia is used in drum experiments, this factor was ruled out. The administration of 1 to 5 mg. of chlorpromazine approximately 20 min. prior to drum trauma increased the survival to 90 per cent, in contrast with the 35 per cent obtained in control cases (TABLE 3). Inasmuch as doses of 2.5 to 5.0 mg. had a clear-cut sedative effect, a comparable degree of sedation was induced by using small amounts of either secobarbital (Seconal), pentobarbital, or morphine. In none of these instances could a protective action be demonstrated. Chlorpromazine not only served to protect against the lethal effects of a standard dose of drum trauma, but it was possible to increase the severity of the trauma considerably without the development of lethal shock. Chlorpromazine-treated rats withstood as much as 1000 revolutions in the Noble-Collip drum with only a 20 per cent mortality, as contrasted with the 100 per cent mortality for control animals. The administration of chlorpromazine after drum trauma had been inflicted had no restorative effect and did not increase the incidence of survival.

A striking feature of the terminal vascular bed of protected animals was the persistance during shock of a reactive hyperemia following temporary obstruction of flow. In the untreated animal subjected to shock, temporary mechanical occlusion resulted in stagnation and an extremely slow return of an active circulation when the occlusion was terminated.

The character of the respiration during the hypotensive period was also modified by chlorpromazine. Respiration of untreated rats during shock was typically rapid, irregular in pattern, and even gasping, with an exaggerated diaphragmatic component. In treated animals, the rate was only moderately faster, it remained regular, and the air-hunger type of gasping did not occur. The preservation of a more normal pattern of respiration during shock suggests that the beneficial action of chlorpromazine may involve a modification of the response of the central nervous system to stress.

In summary, these experiments demonstrated that a number of different agents with a wide spectrum of biological and physiological properties have a favorable influence on the course of the shock syndrome produced by hemorrhage and by drum trauma. Dibenzyline (an adrenergic blocking

TABLE 3

CHLORPROMAZINE IN DRUM SHOCK

	Dose (mg./100 gm.)	Survival	
Controls	—	5/16	31%
Normal rats	2.5	15/16	93%
Adrenalectomy (NaCl)	—	4/15	26%
Adrenalectomy (NaCl)	1.25	2/10	20%
Whole-body X irradiation (650 r)	—	1/16	6%
Whole-body X irradiation (650 r)	1.25	0/12	0
Postdrumming	1.25	0/16	0

drug), chlorpromazine (a central nervous depressant), SC 2159* (a ganglionic blocker), atropine (a cholinergic blocking drug), and azide (a metabolic inhibitor affecting both central and peripheral structures) are effective in this regard. Previous studies have indicated that other blocking drugs showing a mixture of ganglionic and adrenergic blocking potentials, may likewise protect. It is not possible therefore to predict from the known pharmacological action of any single agent the extent to which protection will be afforded. It is probable that the above agents influence biochemical processes as yet unmeasured and that the protection may reside in their effect on basic mechanisms of this nature.

Bacterial Factors

Emphasis has been placed on the harmful effect of bacterial contamination during shock in dogs, both as a consequence of a breakdown in the blood-tissue barrier and of an increased sensitivity of the animal to bacterial products. It has been postulated that the breakdown of bacterial defense mechanisms with an attendant vasculo-toxic sequela represents the decisive factor leading to the development of an irreversible state following severe graded hemorrhage. The validity of this thesis rests in large part on experiments in dogs[20] in which pretreatment with antibiotics successfully circumvented the fatal consequences of a standardized episode of hemorrhagic shock. Further support is derived from a large body of ancillary evidence, pointing to a decreased tolerance to bacterial endotoxins,[13] a fall in blood properdin levels,[21] and an impaired capacity to clear bacteria from the bloodstream during the course of the shock reaction.[22] The basic tenet of the bacterial concept, the causal relationship to irreversibility, has not been confirmed by experiments with antibiotics in other laboratories[23] or by experiments on hemorrhagic shock in the rat.[24] The difficulty of reconciling the experimental findings in the dog with those in the rat constitutes a major problem that must be resolved before the precise significance of the bacterial concept of irreversible shock can be established. There is considerable evidence to indicate that the syndrome follows a similar course in both the rat and the dog, as indicated by direct observations of the peripheral circulation,[25] by studies on tissue metabolism,[26] and by histopathology.[27]

A comparison was made between the incidence of bacteremia* and the over-all response to shock in rats subjected to hemorrhage under conventional laboratory conditions and under conditions of complete asepsis (TABLE 4). Under conventional laboratory conditions, bacterial invasion of the blood, liver, and spleen occurs in 70 to 75 per cent of animals subjected to hemorrhage. The fact that the contaminants were invariably enteric organisms seemed at first glance to support the thesis that shock broke down normal defense barriers and led to invasion of the blood stream

* G. D. Searle & Co., Chicago, Ill.

* These experiments were carried out in collaboration with I. Saphra and W. Antopol, Beth Israel Hospital, New York, N. Y.

Table 4

Relation of Bacteremia to Hemorrhagic Shock

	No. of rats	Positive bact. cultures*	Survival†
Controls	18	2	—
Hemorrhagic shock (conventional conditions)	20	20	8/20
Hemorrhagic shock (aseptic conditions)	12	1	9/12

* Blood, liver, and spleen.
† B.P. 65 mm. Hg for 1 hour; 40 mm. Hg, 2 hours.

from the bowel. However, in experiments carried out under rigid asepsis, no bacterial invasion occurred. This pointed to exogenous factors (handling) and not to the bowel as the source of contamination. The elimination of exogenous contamination led to survival following episodes of hemorrhagic hypotension uniformly lethal under conventional conditions. On the introduction of more drastic hypotensive levels, however, the shock syndrome rapidly progressed to an irreversible state, despite the absence of systemic bacteremia. In traumatic shock, induced by rotating the rats in the Noble-Collip drum, there was no evidence of bacterial contamination despite the lethal and irreversible character of the syndrome. It should also be pointed out that rats subjected to hemorrhage under conventional laboratory conditions, but previously treated with chlorpromazine, were protected against the lethal outcome of the syndrome despite the presence of bacterial contaminants in the blood, liver, and spleen. These experiments support the contention that the bacterial factor in hemorrhagic and traumatic shock is a secondary feature and not necessarily of decisive importance.

The need for more definitive information in this regard stimulated us to set up experiments to determine whether the trend of the shock syndrome in the rat could be altered predictably by bacterial factors. In many respects the rat is a particularly satisfactory experimental animal for this purpose since, in contrast to the dog, bacteria cannot be cultured from tissues such as heart and skeletal muscle, liver, and spleen under normal conditions.

A unique means of establishing the contribution of bacterial elements to the course of the shock syndrome would be the use of animals reared under germ-free conditions. This situation exists only in germ-free colonies of the type maintained at the Lobund Institute of the University of Notre Dame, Notre Dame, Ind. under the direction of James A. Reyniers. A preliminary series of studies of hemorrhagic shock was therefore instituted in 1953 and was continued at intervals through 1954 and 1955.[28] Collaborating in the shock studies on the rat were Helmut A. Gordon and Morris Wagner of the Lobund staff. Inasmuch as an irreversible form of hemorrhagic shock in the rat had been intensively studied by graded bleeding using a self-regulating reservoir technique, this procedure was adopted for study in the experiments with germ-free rats. The initial investigations were concerned with: statistics on survival following blood replacement; blood-loss and blood-uptake values; tissue pathology (gross and

microscopic); and bacteriological cultures of representative tissues and blood specimens.

In general, the findings clearly indicated that the reaction of the germ-free rats to hemorrhage was similar to that of their conventional counterparts (TABLE 5). Germ-free rats tolerated blood loss neither better nor worse than standard rats, when subjected to an episode of drastic hypotension (35 to 40 mm. Hg) for periods of 3 hours. The characteristic pattern of decompensatory uptake of blood from the blood reservoir developed after 1.5 to 2.0 hours of drastic hypotension. Careful bacteriological studies of the apparatus, of the animal tissues, and of the blood specimens failed to indicate any bacterial contamination.

These experiments demonstrated several points clearly: (1) that an irreversible state of shock can be induced by hemorrhage in the absence of bacteremia; (2) that the germ-free rat is not significantly more or less susceptible to blood loss than the controls; and (3) that the collapse of the circulation appears to be associated with the same basic elements in both instances.

Adaptation

Perhaps the most striking experimental form of protection against shock is encountered in the tolerance or resistance engendered in the rat by repeated exposure to sublethal doses of trauma until the adapted animal can withstand extraordinary amounts of drum trauma without fatal consequences.[20] Although considerable study has been given to the physiological basis for the resistant state, no satisfactory explanation for the phenomenon exists. It was felt that important information could be derived from experiments in which factors that increase tolerance to shock were counterbalanced against those agencies that tend to undermine the capacity to withstand shock. Administration of excessive amounts of cortisone for 3 to 4 days produced a marked loss in body weight and a susceptibility to infection, to bacterial endotoxins, and to toxic agents in general. Exposure to LD_{25} to LD_{50} doses of whole-body radiation resulted in a similar impair-

TABLE 5

HEMORRHAGIC SHOCK IN GERM-FREE RATS

	Survival	Blood output %	Blood uptake %
*Group I**			
Conventional	4/6	3.4	0.58
Germ-free	4/6	3.6	0.63
Group II†			
Stock	1/5	2.5	0.66
Monocontaminated‡	2/6	3.6	0.60

* B.P. 65 mm. Hg for 1 hr.; 40 mm. Hg, 2 hr.
† B.P. 65 mm. Hg for 1 hr.; 35 mm. Hg, 2 hr.
‡ Reared under germ-free conditions but harboring a fastidious pleomorphic gram-positive organism.

Table 6

Influence of Blockade of Reticuloendothelial System on Response to Drum Trauma

	Dose (I.V.)	Survival*
Controls	—	10/25 40%
Controls + carbon†	32 mg.	3/27 11%
Trauma-resistant	—	19/20 95%
Trauma-resistant + carbon	32 mg.	5/21 24%

* Controls received 700 turns in drum; trauma-resistant rats, 1000 turns.
† RES-blocking dose administered 2 to 4 hours before trauma.

ment of resistance. Both of these contingencies markedly lowered the capacity of control animals to withstand graded hemorrhage or drum trauma. On the other hand, neither cortisone nor X irradiation altered the resistance of trauma-adapted rats to extraordinarily large doses of drumming. The resistance induced by pretreatment with drugs (chlorpromazine, dibenzyline, hexamethonium, atropine) was, however, completely nullified by cortisone or X irradiation, indicating a basic difference in the factors responsible for the protected state in the two sets of animals.

The adaptation to increasing doses of trauma resembled in many ways other adaptive phenomena, such as those to bacterial endotoxins, to noxious stimuli, and to low oxygen tension. In view of the increasing evidence that these reactions involve stimulation of the reticuloendothelial system (RES) it was evident that there was a need to investigate more directly the relation of the RES to the shock syndrome and to the vascular sequelae of the shock reaction. Both hemorrhagic and traumatic shock were studied, using conventional and resistant animals. In the latter category, animals made resistant by pretreatment with drugs and by adaptation were used.

Blockade of the RES with carbon, thorotrast, or iron served to diminish the capacity of the rat to withstand hemorrhage or trauma (TABLE 6). In the drum experiments, and LD_{50} dose now became an LD_{90} dose.[30] In hemorrhagic shock, there was a marked exaggeration of the decompensatory tendency and a failure to respond to blood replacement measures. A significant proportion of the animals succumbed before the end of the standard 3-hour period of hypotension.

All of the agencies that predispose control animals to shock also counteracted the beneficial action or protection of pharmacological materials (TABLE 7). In contrast, the trauma-resistant animals were not deleteriously

Table 7

Protection Against Drum Trauma

	Drug-protected (2.5 mg. chlorpromazine) Survival*		Trauma-resistant Survival	
Controls	23/25	92%	28/30	93%
10 mg. cortisone 3 days	2/12	16%	13/15	86%
Whole-body irradiation (750 r) 7 days postirradiation	3/15	20%	10/12	83%
Blockade of RES (carbon)	4/20	20%	5/20	25%

* Rats received 850 turns in the Noble-Collip drum.

affected by such drastic measures as the administration of high doses of cortisone, X irradiation, dietary restriction (low protein diet), and adrenalectomy. The only procedure that uniformly abolished the state of resistance was blockade of the reticuloendothelial system by means of colloidal agents such as carbon, thorotrast, or saccharated iron. Loss of resistance was manifest within 1 to 2 hours after blockade had been established, and persisted for approximately 4 to 6 hours. Thereafter, the trauma-resistant state was restored rapidly and was effectively sustained.

These experiments bring into sharp focus an area of homeostasis, the reticuloendothelial system, whose functional activities are only poorly understood but whose obvious importance presents us with a challenge that must be met.

The development of the aseptic-hemorrhagic shock procedure in the rat makes it possible to study the evolution of the shock syndrome in the absence of systemic bacteremia. The method also provides an opportunity to investigate a possible protective action of antibiotics independently of their antibacterial potential. The experiments indicated that orally administered Aureomycin had a further salutary effect on the capacity of such rats to withstand hemorrhagic hypotension (TABLE 8). An unusually high survival rate was obtained with a combined aseptic Aureomycin regimen. Since there was no demonstrable bacteremia, the beneficial action was due either to the suppression of bacterial endotoxins formed in the bowel, to a blunting of their vasculotoxic action, or to some unknown metabolic effect of Aureomycin.

In this regard, experiments were conducted with the endotoxins of gram-negative bacteria, using these agents either as predisposing elements or as a means of inducing resistance or tolerance. Small sublethal doses of lipopolysaccharides (*Escherichia coli* extracts) were administered just preceding the occurrence of hemorrhagic or traumatic shock. Following these procedures endotoxin-pretreated rats went into profound shock, were refractory to blood replacement measures, and showed a much higher mortality. The endotoxin-treated animals remained susceptible to shock even when treated with doses of autonomic blocking drugs that were normally protective.

It is possible to build up a tolerance to the biological action of endotoxins by injection at daily intervals of successively higher doses until even lethal doses can be overcome.[31] It was of interest to determine whether this

TABLE 8

BACTERIAL FACTORS IN RATS SUBJECTED TO HEMORRHAGIC SHOCK

	Survival*		Blood output %	Blood uptake %
Conventional conditions	7/20	35%	3.2	0.25
Rigid asepsis	12/22	55%	3.5	0.20
Asepsis + Aureomycin†	11/12	90%	3.45	0.15

* B.P. at 65 mm. Hg for 1 hour; 35 mm. Hg for additional 2 hours.
† 150 mg. daily in divided doses orally for 5 days.

form of tolerance or adaptation conferred a capacity to resist traumatic or hemorrhagic shock. Rats were therefore treated with *E. coli* extracts for 4 to 5 days and subjected to drum shock 72 hours later, when tolerance should be at its maximum. A series of small doses of endotoxin effectively protected rats against lethal hemorrhage and drum trauma. Higher doses of endotoxin exerted no such protective action. Whether endotoxin treatment induces a specific form of adaptation or whether it initiates a general hypertrophy of systems such as the RES is, of course, unknown, and the question presents an important field for future study.

References

1. Baez, S., B. W. Zweifach & E. Shorr. 1952. Federation Proc. **11**: 7.
2. Hershey, S. G., B. W. Zweifach & D. B. Metz. 1954. Anesthesiology. **15**: 589.
3. Fine, J. 1952. Shock and Vascular Homeostasis: 123. 2nd Conf. Josiah Macy, Jr. Foundation. New York, N. Y.
4. Zweifach, B. W., R. Chambers, R. E. Lee & C. Hyman. 1948. Ann. N. Y. Acad. Sci. **49**(4): 553.
5. Zweifach, B. W., S. G. Hershey, E. A. Rovenstine, R. E. Lee & R. Chambers. 1945. Surgery. **18**: 1948.
6. Fine, J. 1954. The Bacterial Factor in Traumatic Shock. C. C. Thomas. Springfield, Ill.
7. Engel, F. L. 1952. Shock and Vascular Homeostasis: 26. 2nd Conf. Josiah Macy, Jr. Foundation. New York, N. Y.
8. Wiggers, C. J. 1950. Physiology of Shock. Commonwealth Fund. New York, N. Y.
9. Folkow, B. 1955. Physiol. Revs. **35**: 629.
10. Zweifach, B. W. & D. B. Metz. 1955. Am. J. Physiol. **182**: 155.
11. Russell, J. A., C. N. H. Long & A. E. Wilhelmi. 1944. J. Exptl. Med. **79**: 23.
12. Wiggers, C. J. 1942. Physiol. Revs. **22**: 74.
13. Fine, J. 1956. Shock and Vascular Homeostasis. 5th Conf. Josiah Macy, Jr. Foundation. New York, N. Y.
14. Laborit, H. 1956. Ergeb. Med. Grundlagenforsch. **217**: 546.
15. Remington, J. W., W. F. Hamilton, G. H. Boyd, W. F. Hamilton, Jr. & H. M. Cadell. 1950. Am. J. Physiol. **161**: 117.
16. Zweifach, B. W., S. Baez & E. Shorr. 1952. Federation Proc. **11**: 177.
17. Kelan, M. & B. W. Zweifach. 1954. Surg. Gynecol. Obstet. **99**: 707.
18. Hershey, S. G., B. W. Zweifach & W. Antopol. 1955. Anesthesiology. **17**: 256.
19. Laborit, H. 1954. Arch. Exptl. Pathol. Pharmakol. **222**: 41.
20. Fine, J. 1951. Symposium on Shock. Chap. 5. Army Medical Service Graduate School, Washington, D. C.
21. Frank, E., J. Fine & L. Pillemer. 1955. Proc. Soc. Exptl. Biol. Med. **89**: 223.
22. Schweinburg, F. B. & J. Fine. 1955. Proc. Soc. Exptl. Biol. Med. **88**: 589.
23. DeBakey, M. E. 1956. Shock and Vascular Homeostasis. 5th Conf. Josiah Macy, Jr. Foundation. New York, N. Y.
24. Lin, K., S. G. Hershey & B. W. Zweifach. Unpublished data.
25. Zweifach, B. W., R. E. Lee, C. Hyman & R. Chambers. 1944. Ann. Surg. **120**: 232.
26. Engel, F. L., H. C. Harrison & C. N. H. Long. 1944. J. Exptl. Med. **79**: 9.
27. Moon, V. 1942. Shock: Its Dynamics, Occurrence and Management. Lea & Febiger. Philadelphia, Pa.
28. Zweifach, B. W. 1956. Shock and Vascular Homeostasis. 5th Conf. Josiah Macy, Jr. Foundation. New York, N. Y.
29. Noble, R. L. & J. B. Collip. 1942. Quart. J. Exptl. Physiol. **31**: 187.
30. McKenna, J. M. & B. W. Zweifach. 1957. Am. J. Physiol. **187**: 263.
31. Thomas, L. 1954. Ann. Rev. Physiol. **16**: 467.

Printed in the United States of America

MONOGRAPHIC PUBLICATIONS

OF

THE NEW YORK ACADEMY OF SCIENCES

(Lyceum of Natural History, 1817–1876)

(1) The Annals (octavo series), established in 1823, contain the scientific contributions and reports of researches, together with the records of meetings of the Academy. The articles that comprise each volume are printed separately, each in its own cover, and are distributed immediately upon publication. The price of the separate articles depends upon their length and the number of illustrations, and may be ascertained upon application to the Executive Director of the Academy.

Current numbers of the Annals are sent free to all Members of the Academy desiring them.

(2) The Special Publications, established in 1939, are issued at irregular intervals as cloth-bound volumes. The price of each volume will be advertised at time of issue.

(3) The Memoirs (quarto series), established in 1895, are issued at irregular intervals. It is intended that each volume shall be devoted to monographs relating to some particular department of science. Volume I, Part 1 is devoted to Astronomical Memoirs, Volume II to Zoological Memoirs. No more parts of the Memoirs have been published to date. The price is one dollar per part.

(4) The Scientific Survey of Porto Rico and the Virgin Islands (octavo series), established in 1919, gives the detailed reports of the anthropological, botanical, geological, paleontological, zoological, and meteorological surveys of these islands.

Subscriptions and inquiries concerning current and back numbers of any of the publications of the Academy should be addressed to

EXECUTIVE DIRECTOR
The New York Academy of Sciences
2 East Sixty-third Street
New York 21, N. Y.